Camphor-Derived, Chelating Auxiliaries for the Highly Diastereoselective Intermolecular Pauson−Khand Reaction: Experimental and Computational Studies

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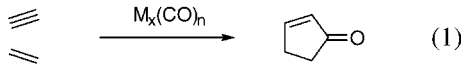
A family of enantiomerically pure (2*R*)-10-(alkylthio)isoborneols [methylthio (**1**), neopentylthio (**2**), phenylthio (**3**)], specifically designed as chiral auxiliaries suitable for chirality transfer to cobalt in Pauson−Khand reactions, has been synthesized. The dicobalt hexacarbonyl complexes of the alkoxyacetylenes derived from these alcohols (**10a**−**12a**) can be converted to the rather stable, internally chelated, pentacarbonyl complexes **10b**−**12b** by treatment with NMO. The intermolecular Pauson−Khand reactions of **10b**−**12b** with strained olefins take place with synthetically useful rates at low temperatures (down to −20 °C), with high yields and diastereoselectivities: norbornene (77%; 92:8), norbornadiene (82%; 96:4), bicyclo[3.2.0]hept-6-ene (91%; 93:7). The major diastereomer of the adduct of **10b** with norbornadiene, **14**, has been used as the starting point for a synthesis of (*S*)-(−)-4-alkyl-2-cyclopentenones through a sequence consisting of completely diastereoselective conjugate addition, reductive cleavage with recovery (>95%) of the chiral auxiliary, and retro Diels−Alder reaction. The stereochemical course of the reaction of **10b** with norbornadiene has been analyzed and rationalized by theoretical means by using a combined semiempirical [PM3-(tm)]/density functional theory [VWN−Perdew-Wang 91] approach.

Introduction

The metal-mediated cyclocondensations[1] between an alkyne, an alkene, and a CO fragment probably represent the most versatile methodology for the construction of cyclopentenone skeletons (eq 1).[2]



(1)

Among these methods, the Pauson−Khand reaction [$M_x(CO)_n = Co_2(CO)_8$][3] stands out because of its experimental simplicity, functional group compatibility, and predictable regio- and stereochemical outcome and has consequently found widespread use in total synthesis.[4] It is thus not surprising that increasing efforts are being devoted to the development of practical enantioselective versions of the reaction. Two main approaches have been followed with this aim: The use of chiral auxiliaries directly bound to either of the reacting fragments[5] and the intermediate generation of complexes possessing a

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(1) For representative examples of metal-mediated cyclocondensations leading to five-membered carbocycles, see the following. Ti: (a) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688−11689. (b) Hicks, F. A.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 9450−9451. Zr: (c) Agnel, G.; Negishi, E.-I. *J. Am. Chem. Soc.* **1991**, *113*, 7424−7426. Mo: (d) Jeong, N.; Lee, S. J.; Lee, B. Y.; Chung, Y. K. *Tetrahedron Lett.* **1993**, *34*, 4027−4030. (e) Kent, J. L.; Wan, H. H.; Brummond, K. M. *Tetrahedron Lett.* **1995**, *36*, 2407−2410. W: (f) Hoye, T. R.; Suriano, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1154−1156. Fe: (g) Pearson, A. J.; Dubbert, R. A. *Organometallics* **1994**, *13*, 1656−1661. Ru: (h) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187−6188. Ni: (i) Tamao, K.; Kobayashi,. K.; Ito, Y. *Synlett* **1992**, 539−546. (j) Pagés, L.; Llebaria, A.; Camps, F.; Molins, E.; Miravitlles, C.; Moretó, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 10449−10461. (k) Zhang, M. H.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498−4499.

(2) For reviews on cyclopentannelation reactions, see: (a) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141−170. (b) Ramaiah, M. *Synthesis* **1984**, 529−560. (c) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Berlin, 1987. (d) Hudlicky, T.; Price, J. *Chem. Rev.* **1989**, *89*, 1467−1486.

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(4) For some recent examples, see: (a) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353−4363. (b) Thommen, M.; Keese, R. *Synlett* **1997**, 231−240. (c) Deoliveira, C. M.; Ferracini, V. L.; Foglio, M. A.; de Meijere, A.; Marsaioli, A. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1833−1839. (d) Donkervoort, J. G.; Gordon, A. R.; Johnstone, C.; Kerr, W. J.; Lange, U. *Tetrahedron* **1996**, *52*, 7391−7420. (e) Paquette, L. A.; Borrelly, S. *J. Org. Chem.* **1995**, *60*, 6912−6921. (f) Yoo, S. E.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968−6972. (g) Krafft, M. E.; Wright, C. *Tetrahedron Lett.* **1992**, *33*, 151−152. (h) Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853−6861. (i) Takano, S.; Inomata, K.; Ogasawara, K. *Chem Lett.* **1992**, 443−446.

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disymmetric C_2Co_2 core.[6] Despite the conceptual appeal inherent to the second approach, only the first one has found application in the synthesis of complex molecules.[5b,7] This is probably due to practical reasons; thus, the preparation of diastereomerically pure (alkyne)Co_2-$(CO)_5$L* complexes normally involves lengthy procedures and/or tedious chromatographic separations.

During the past few years, we have systematically explored the use of chiral alcohols as stereochemical controllers in the Pauson−Khand reaction.[5a−e] For the intramolecular process, the use of either *trans*-2-phenylcyclohexanol (as an enol ether with trans configuration)[5b,d] or 3-(neopentyloxy)isoborneol (as an ynol ether)[5c] allows the achievement of high levels of diastereoselectivity in the process. On the other hand, a systematic scrutiny of the usual arylcyclohexyl and camphor-based auxiliaries has not allowed the identification of similarly efficient controllers for the intermolecular process.[5e]

In an attempt to generate a satisfactory solution for this more stereochemically demanding situation, and bearing in mind the work by Krafft on the directed Pauson−Khand reaction,[8] we started thinking about a new type of chiral controller, specifically suited for the Pauson−Khand cycloaddition, that could combine the main advantages of the two approaches to stereocontrol discussed earlier. A chiral auxiliary with chelating capacity could display a dual role in the reaction: It could allow an efficient transfer of chirality to the C_2Co_2 cluster and could secure the diastereoselectivity of the process by directing the reaction toward one of the two diastereotopic cobalt atoms (Figure 1).

Previous experience with alkoxyacetylenes[9] and the ready availability of their dicobalt hexacarbonyl complexes[10] suggested oxygen as the linking element (X in Figure 1). On the other hand, the specification of sulfur as the element planned for interaction with cobalt offered significant advantages over other possible candidates such as phosphorus. First, the ability of sulfur to stabilize coordinatively unsaturated cobalt species had been well established by Krafft.[8] Second, the rather labile nature of the Co−S dative bond[11] should greatly facilitate the dissociative equilibrium B (Figure 1), thus contributing to a rate enhancement in the overall process.

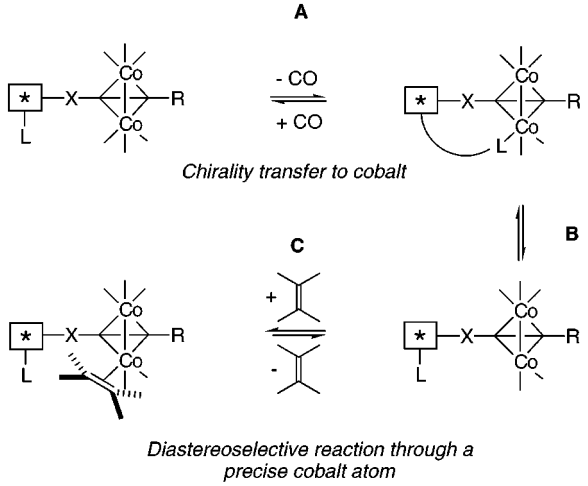

Figure 1. Stereocontrol in Pauson−Khand reactions with chelating auxiliaries.

We report in the present paper full details of the successful use in Pauson−Khand chemistry of a family of camphor-derived chiral auxiliaries **1**−**3** designed according to the principles we have just discussed.[12] The origin of the diastereoselectivity observed when using this new family of chelating auxiliaries is analyzed and rationalized by means of theoretical (semiempirical and DFT) calculations on one of the actual systems involved in the study.

Results and Discussion

Chiral Controllers and Alkoxyacetylene Precursors. Simple modeling studies, confirmed by preliminary experiments, suggested that 3-(alkylthio) alcohols presented an optimal distance between functional groups for the desired chelation.[13] Although these alkylthio alcohols could be generally available from enantiomerically pure α,β-unsaturated ketones by conjugate thiol addition and carbonyl reduction,[14] the requirements of both enantio- and diastereomeric purity in our target molecules along with the desire for structural rigidity greatly reduced the scope of possible candidates.

In this context, we thought that (2*R*)-10-mercaptoisoborneol (**4**), ultimately available in enantiomerically pure form from inexpensive D-camphorsulfonic acid,[15] was an ideal template for the planned intermolecular Pauson−Khand reactions since, by simply tuning the electronic and steric nature of the sulfide substituent, we should be able to maximize the diastereoselectivity of the process. Along with the known (2*R*)-10-(methylthio)-isoborneol (**1**),[16] we undertook the synthesis of two new

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(13) Preliminary studies performed with the dicobalt hexacarbonyl complexes of the alkoxyacetylenes derived from *trans*-2-phenylthiocyclohexanol and *trans*-2-(*tert*-butylthio)cyclohexanol did not provide any evidence of chelation (see the following text in the paper).

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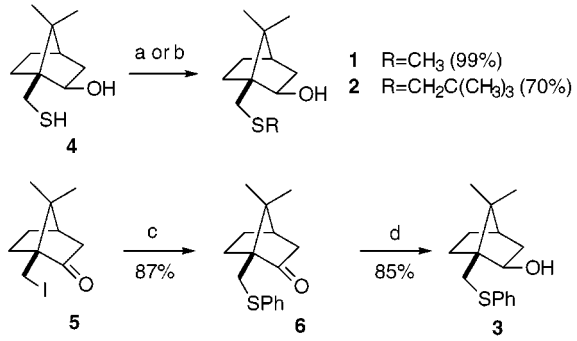
Scheme 1[a]



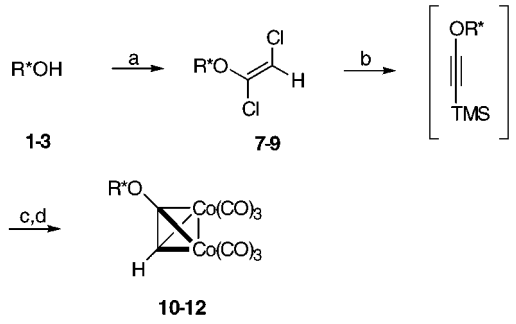
[a] Key: (a) MeI, MeONa/MeOH; (b) (1) NaH/THF, (2) $BrCH_2C(CH_3)_3$, HMPA, Δ; (c) PhSNa, HMPA/THF, Δ; (d) $LiAlH_4$, Et_2O.

chelating auxiliaries, (2*R*)-10-(neopentylthio)isoborneol (**2**) and (2*R*)-10-(phenylthio)isoborneol (**3**) displaying larger and electronically different substituents on sulfur. Thus, (2*R*)-10-mercaptoisoborneol (**4**), prepared from camphorsulfonyl chloride by reduction with lithium aluminum hydride,[15] was submitted to regioselective alkylation with methyl iodide and neopentyl bromide to afford **1** and **2** in high yield, respectively (Scheme 1). For the preparation of 10-(phenylthio)isoborneol (**3**), 10-iodocamphor (**5**)[17] was first reacted with sodium thiophenolate in the presence of HMPA to afford 10-(phenylthio)-camphor (**6**) in 87% chemical yield. Reduction of ketone **6** with $LiAlH_4$ in ether afforded a 10/1 mixture of exo and endo alcohols from which the target molecule **3** could easily be separated in 85% yield by standard column chromatography.

With the chiral auxiliaries in hand, we proceeded to test their efficiency in the intermolecular Pauson−Khand reaction. As a first step, the corresponding alkoxyacetylenes and their dicobalt hexacarbonyl complexes had to be prepared. Alkoxyacetylenes derived from chiral secondary alcohols are usually prepared by a one-pot sequence starting from trichoroethylene,[9b] while the formation in high yield of their dicobalt hexacarbonyl complexes requires the intermediate silylation of the acetylenic hydrogen.[10] In the present instance, however, we found that much better results are obtained if the isolation of the alkoxyacetylenes is obviated and their precursor (*E*)-alkoxydichloroolefins are used as synthetic intermediates. To do that, the original procedures were slightly modified as follows: The starting chiral alcohols **1**−**3** were deprotonated with KH and reacted with trichloroetylene in THF to afford the (*E*)-alkoxydichloroalkenes **7**−**9** in high yield (Scheme 2 and Table 1). These are stable intermediates and can be stored for several weeks at room temperature without noticeable decomposition. From the dichloroolefins, a four-reaction transformation consisting of hydrogen chloride elimination/transmetalation with *n*-BuLi in diethyl ether, silylation with TMSCl, complexation ($Co_2(CO)_8$/hexane), and deprotection (K_2CO_3/ MeOH) was performed in a single synthetic operation leading to the target dicobalt hexacarbonyl complexes **10**−**12** in high overall yields.

Behavior of the Dicobalt Hexacarbonyl Complexes: Generation of Internally Chelated Species. The chelating ability of this new kind of auxiliary was

Scheme 2[a]

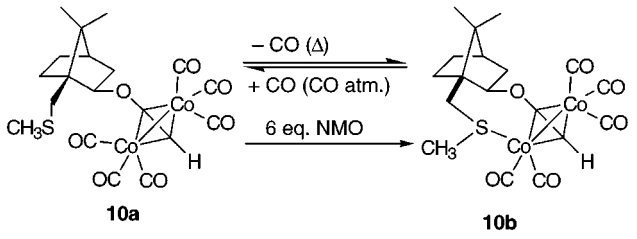


[a] Key: (a) $CHCl{=}CCl_2$, KH, THF; (b) *n*-BuLi, Et_2O, TMSCl; (c) $Co_2(CO)_8$, hexane; (d) K_2CO_3, MeOH.

Table 1. Synthesis of Dicobalt Hexacarbonyl Complexes of Alkoxyacetylenes 1−3

R*OH	olefin (yield, %)	complex (yield, %)
1	**7** (78)	**10** (62)
2	**8** (74)	**11** (72)
3	**9** (77)	**12** (71)

Scheme 3



soon made evident. Thin-layer chromatography of the original red hexacarbonyldicobalt complexes revealed the presence of a minor component, characterized by a less intense dark-brown spot at a lower R_f. In the case of the complex containing the 10-(methylthio)isoborneol auxiliary (**10a**), for instance, when a hexane solution of the red hexacarbonyl complex was heated at 50 °C under a nitrogen stream (CO purge), the intensity of the lower brown spot increased while that of the red upper one decreased. Conversely, when the resulting mixture of complexes was cooled back to room temperature under a CO atmosphere, the brown compound reverted to the original red hexacarbonyl complex **10a**. This is consistent with an equilibrium between a hexacarbonyl **10a** and a pentacarbonyl chelated form **10b** of the corresponding (alkoxyacetylene)dicobalt complex, as shown in Scheme 3.[18]

^{1}H NMR analysis (C_6D_6, 25 °C) of **10a**/**10b** equilibrium mixtures (Figure 2) disclosed some interesting data. Upon chelation, the acetylenic proton experienced an upfield shift from its original δ 5.25 ppm in the parent hexacarbonyl complex to δ 4.94 ppm in the chelated species. This is in accordance with a substitution of an electroacceptor CO group for a more donating sulfide ligand on cobalt. Similar shifts in the ^{1}H NMR spectrum have been reported in the literature for alkyne−$Co_2(CO)_5(PR_3)$ clusters.[19] Perhaps even more revealing are the

(16) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222−4224.

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(18) Parallel behavior has been observed by Krafft and co-workers in the dicobalt hexacarbonyl complex of a bis-homopropargylic thioether (see ref 8e).

(19) Dunn, J. A.; Pauson, P. L. *J. Organomet. Chem.* **1991**, *419*, 383−389.

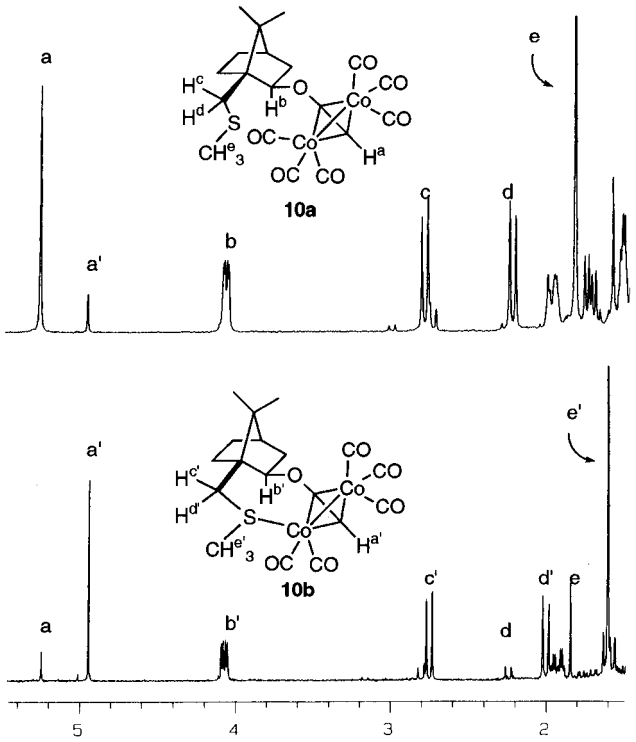


Figure 2. Portions of the ^{1}H NMR spectra (300 MHz, C_6D_6) of **10a** and **10b** showing the main changes associated with the internal chelation process.

variations in chemical shift displayed by the methyl ($-SCH_3$) and methylene ($-CH_2SR$) groups directly attached to sulfur. In the hexacarbonyl complex **10a**, the singlet signal corresponding to the methyl group ($-SCH_3$) appears at δ 1.84 ppm and at δ 1.60 ppm in **10b**. The methylene ($-CH_2SR$) AB system in **10a** displays resonances at δ 2.24 and 2.80 ppm, while the chelated complex **10b** shows the same signals at δ 2.00 and 2.75 ppm, respectively.[18] Further evidence supporting a chelation process could be found in the mass spectrum (CI-NH_3) of **10a**. Along with the peak corresponding to the molecular ion of the parent hexacarbonyl complex plus ammonia at m/e = 528 (M^+ + 18, 25), a more intense signal m/e = 483 (M^+ − CO + 1, 80) due to the loss of one CO unit is found. It is to be noted that the mass spectra of dicobalt hexacarbonyl complexes of alkoxyacetylenes derived from nonchelating alcohols, when recorded under similar conditions, do not exhibit any significant peak corresponding to CO loss.

Although two diastereomers can exist for **10b**, depending on which of the diastereotopic cobalt atoms is involved in the chelation process, the NMR observations discussed above tend to indicate the highly predominant existence of a single diastereomer.

While we could shift the equilibrium between **10a** and **10b** toward the chelated form (vide supra) by thermal activation, we were unable to do so in a complete fashion. A maximum 85:15 ratio of chelated and unchelated complexes was achieved on heating the solution of the parent hexacarbonyl complex at 50 °C for 1 h with CO removal. Longer heating times did not lead to any improvement in the **10a**/**10b** ratio and were deletereous for complex recovery. Most likely, complex decomposition affords free carbon monoxide, which reacts with **10b** to give back **10a**, thus preventing complete conversion.

Scheme 4

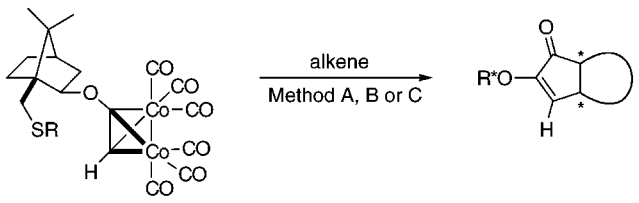


Table 2. Intermolecular Pauson−Khand Reactions Using Chelating Auxiliaries

Entry	R	Alkene	Pauson-Khand Adduct	Reaction Conditions	T (°C)	Yield (%)	de (%)
1	CH_3		**13**	A	r.t.	65	40
2				B	0	66	76
3				B	-20	77	84
4				C	50	69	20
5				C	0	99	60
6	CH_3		**14**	A	r.t.	95	20
7				B	−20	82	**92**
8	CH_3		**15**	A	50	70	44
9				B	−20	91	86
10	$CH_2C(CH_3)_3$		**16**	B	−20	61	92
11	C_6H_5		**17**	B	−20	65	86

For reactivity studies, a complete conversion of **10a** into **10b** was clearly required. We could finally succeed at this goal by treating **10a** with *N*-methylmorpholine *N*-oxide (NMO); thus, addition of 6 equiv of NMO to a CH_2Cl_2 solution of the hexacarbonyl complex **10a** under nitrogen resulted in the total formation of the chelated species (Scheme 3). In fact, it is known that amine oxides, like NMO[20] or TMAO,[21] are efficient promoters of the Pauson−Khand reaction. Most probably, these reagents act by oxidizing a coordinated CO ligand to CO_2,[22] thus providing an empty coordination site for the incoming olefin. In the present case, the irreversible character of the CO oxidation prevents the regeneration of the starting hexacarbonyl complex **10a**, thus allowing its complete conversion.

A similar behavior was observed in the 10-(neopentylthio)isoborneol-containing complex **11a** and in its phenylthio analogue **12a**, thus confirming the importance of molecular architecture for the internal chelation process.

Pauson−Khand Cyclizations. Once we were acquainted with how to control the equilibrium between the hexacarbonyl (**a**) and the chelated pentacarbonyl (**b**) forms of complexes **10**−**12**, we proceeded to test their efficiency in the intermolecular Pauson−Khand reaction with strained alkenes (Scheme 4). The results of this study are collected in Table 2.

Our first goal was to identify the effect on diastereoselectivity of preforming the chelated pentacarbonyl species. Reaction conditions A, consisting of working in hexane solution under a CO atmosphere and performing

(20) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292.
(21) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. *Synlett* **1991**, *6*, 204−206.
(22) (a) Albers, M. O.; Coville, N. J. *Coord. Chem. Rev.* **1984**, *53*, 227−259. (b) Shen, J.-K.; Gao, Y.-C.; Shi, Q.-Z.; Basolo, F. *Organometallics* **1989**, *8*, 2144−2147.

the reaction by thermal activation, would ensure a maximum concentration of **a**-type complexes. This does not necessarily mean that **b**-type complexes do not participate as intermediates in the reactions but probably ensures that **b**-type complexes, if formed, will immediately react with the partner olefin without accumulation in the reaction medium or stereochemical equilibration between diastereomers. According to our expectations, when complex **10a** was treated with norbornene under conditions A at room temperature, no **10b** could be observed by TLC of the reaction mixture. The corresponding cycloadduct **13** was isolated after 4 h in 60% yield and with rather low (40%) diastereomeric excess (Table 2, entry 1).

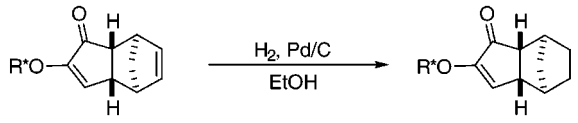
Alternatively, reaction conditions B, consisting in reacting the starting mixture of complexes with 6 equiv of NMO in dichloromethane at room temperature, cooling the mixture to a given temperature and then adding the partner olefin, would ensure that the reaction takes place through **b**-type complexes. In this way, addition of 6 equiv of NMO to a solution of **10a** in CH_2Cl_2 at room temperature resulted, after 10 min, in the complete formation of **10b**, as monitored by TLC. When the resulting solution was cooled to 0 °C and norbornene was added at that temperature, **13** was obtained in 66% yield with 76% de (Table 2, entry 2). Most remarkably, by using these conditions we were able to lower the reaction temperature down to −20 °C. At this temperature, the reaction proceeded to completion overnight to afford cyclopentenone **13** in 77% yield and 84% de (Table 3, entry 3). Interestingly enough, the diastereomers of **13** are separable by simple column chromatography. Attempts at further lowering the cyclization temperature were unsuccessful, with no conversion to the desired cyclopentenone being observed after 24 h at −40 °C.

In an attempt to simplify the experimental procedure for the generation of **b**-type complexes, the purely thermal dissociation of CO was also considered and used in reaction conditions C. These consisted in displacing the equilibrium toward **b** by heating a hexane solution of the starting hexacarbonyl complex at 50 °C for 1 h. This solution was then cooled to the desired temperature, and the reacting alkene was added. Following this protocol, norbornene addition to a hexane solution of **10b**/**10a** (ca. 85/15) at 50 °C yielded almost instantaneously (10 min) cycloadduct **13**, albeit in a disappointing 20% de (Table 2, entry 4). When the cyclization temperature was lowered to 0 °C, an almost quantitative yield of **13** was recorded, but the diastereomeric excess was only 60% (Table 2, entry 5).

When the experiments performed under conditions B and C at the same temperature (0 °C) are compared, it is clear that higher diastereoselectivities are recorded under conditions B. This can probably be attributed to the fact that, under conditions C, some **a**-type complex remains in the reaction medium, and as we have seen in entry 1, its reaction with norbornene is poorly selective. According to this, only conditions B were used for the generation of **b**-type complexes in further experiments.

Reaction of **10** with other strained alkenes under conditions B afforded the corresponding adducts in good yield and excellent diastereoselectivities. *In the most favorable case, reaction with norbornadiene at −20* °C (Table 2, entry 7) afforded ***14*** *in 82% yield and with 92% diastereomeric excess*. Again, the diastereomers turned out to be readily separable by column chromatography.

Scheme 5



14 (major diastereomer) **13 (X-Ray)**

As we will see later, these results are of great significance since **14** has been used as the starting point for an enantioselective synthesis of 4-substituted 2-cyclopentenones. Likewise, reaction with bicyclo[3.2.0]hept-6-ene, a slightly less reactive olefin, provided **15** in 91% yield and 86% de (Table 2, entry 9). On the other hand, chiral auxiliaries with more sterically demanding sulfide-chelating fragments did not induce higher stereoselectivities in the reaction. Cycloaddition of **11**, bearing a (neopentylthio)methyl moiety, with norbornadiene (Table 2, entry 10) afforded adduct **16** in 92% de, exactly the same diastereoselectivity displayed by **10**, but in significantly lower yield. The Pauson−Khand reaction of **12**, bearing a (phenylthio)methyl chelating handle, shows a slightly lower (86% de) diastereoselectivity (Table 2, entry 11).

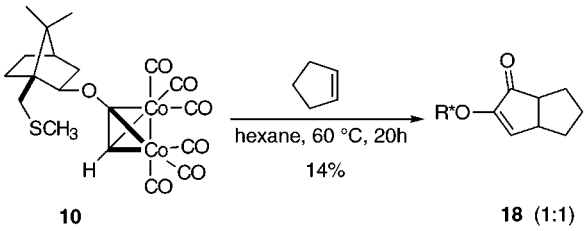
These results clearly show that neither the steric bulk nor the electronic nature of the group attached to sulfur[23] exerts a significant influence on the diastereoselectivity of the reactions. With respect to yield, it is clear that the smaller methyl group displays optimal characteristics, thus defining **1** as the chiral controller of choice for this chemistry. A distinct characteristic of all of the chelating controllers is that they undergo the Pauson−Khand reactions with strained olefins with synthetically useful rates at the low temperature of −20 °C.

The absolute configuration of the major diastereomer of **13** could be established by X-ray crystallography,[12] following isolation by flash chromatography and crystallization from cold pentane, as the one depicted in Scheme 5. The crystal structure revealed that the absolute configuration of the newly formed stereogenic centers in **13** is 1*R*,2*R*,6*R*,7*R*. It also confirmed an exo fusion between the cyclopentenone and norbornene moieties as expected on the basis of the normal face selectivity of Pauson−Khand reactions. Moreover, we were able to correlate the configurations of the major diastereomers of **13** and **14**. Thus, when the nonconjugated double bond in the major diastereomer of **14** was selectively hydrogenated over Pd/C in ethanol (Scheme 5), the product obtained was spectroscopically (^{1}H and ^{13}C NMR) identical with the major diastereomer of **13**.

The high reactivity exhibited by pentacarbonyl complex **10b** could not be satisfactorily exploited for reactions with less reactive olefins. For example, when **10** was submitted to cyclization with cyclopentene using NMO activation (reaction conditions B), no Pauson−Khand adduct could be detected in the final reaction mixture. We attribute this to a low stability of the chelated complex **10b** or its olefin-coordinated derivative in the CH_2Cl_2/NMO mixture: In the absence of a sufficiently reactive alkene (i.e., one giving an olefin-coordinated complex that readily evolves into a product-forming cobaltacycle), complex **10b** slowly decomposes leading to a mixture of unidentified products. Nevertheless, cyclization with

(23) According to PM3 calculations, the electron density at sulfur in alcohols **1**−**3** varies in the order **2** > **1** > **3**.

Scheme 6



cyclopentene could be achieved, albeit in low yield (14%), by thermal activation at 60 °C in a sealed tube under nitrogen (Scheme 6). Unfortunately, ^{1}H NMR analysis of the resulting cyclopentenone **18** revealed a 1:1 mixture of diastereomers.

Synthesis of Enantiopure 4-Substituted 2-Cyclopentenones. Although the cyclopentane ring is widespread among chiral natural products, and much effort has been devoted to the enantioselective construction of five-membered carbocycles,[24] general methods for the enantioselective synthesis of substituted cyclopentenones are scarce,[24a,b] and the preparation of these compounds still relies on enzymatic kinetic resolutions or involves the use of chiral starting materials.[25] In view of this, we planned to use **14** as a versatile new entry to the enantiopure cyclopentanoid core. Several features convert **14** in an optimal starting point for this purpose: First, the chiral auxiliary **1** used in its synthesis can be easily prepared on a multigram scale; second, **14** is formed in high yield in a highly diastereoselective fashion and can be easily brought to diastereomeric purity; finally, the norbornene core in **14** should exert valuable substrate stereocontrol from which addition reactions to the α-alkoxycyclopentenone should benefit and can easily be removed by retro Diels–Alder methodology. Thus, starting from **14**, a three-step sequence consisting of conjugate addition, chiral auxiliary removal, and retro Diels–Alder reaction (Figure 3) should readily produce enantiomerically pure 4-alkyl-2-cyclopentenones.

To demonstrate the feasibility of this protocol, we examined each of these transformations. After a range

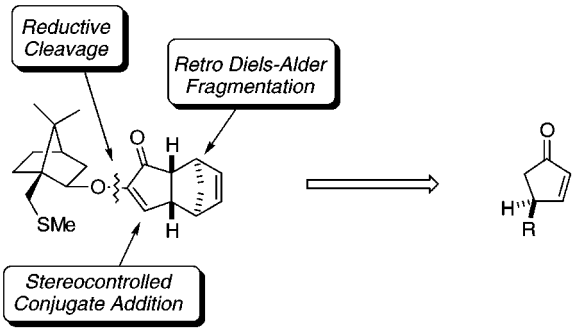
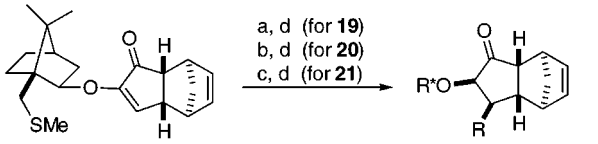


Figure 3. Synthetic strategy for the synthesis of enantiomerically pure (*S*)-4-substituted-2-cyclopentenones from adduct **14**.

Scheme 7[a]



14

19 R= Me (80%)
20 R= *n*-Bu (81%)
21 R= Ph (66%)

[a] Key: (a) $(CH_3)_2CuLi$, TMSCl, ether, −10 °C; (b) $(n\text{-}Bu)_2Cu(CN)Li_2$, TMSCl, ether, −10 °C; (c) Ph_2CuLi, TMSCl, ether, rt; (d) 0.1 equiv of NBu_4F, THF, 0 °C.

of conditions for conjugate addition to **14** were explored,[26] the use of cuprates [Me_2CuLi, prepared at low-temperature according to Bertz,[27] $Bu_2Cu(CN)Li_2$,[28] and Ph_2CuLi, prepared from $CuBr_2{\cdot}SMe_2$] in the presence of trimethylsilyl chloride (TMSCl)[29] were found to give the best results. Under these conditions, the addition reactions were completely stereoselective, leading in high yield, after deprotection of the intermediate silyl enol ethers with a catalytic amount of fluoride (0.1 equiv of NBu_4F, THF, 0 °C),[30] to configurationally pure *cis*-α-alkoxy-*β*-alkylcyclopentanone derivatives **19**–**21** (Scheme 7). The cis stereochemistry in these α-alkoxy ketones was deduced from the coupling constant between the α-alkoxy and α-alkyl protons (J = 11 Hz, $CDCl_3$). Conveniently, if the conjugate additions are performed on the diastereomeric mixtures directly arising from the Pauson–Khand reactions, minor diastereomers of the addition products can be chromatographically removed with great ease; in practice, it is advisable to perform the separations at this point of the synthetic sequence.

Subsequent auxiliary removal was effected by reductive cleavage with samarium diiodide[31] in THF/MeOH (Scheme 8). An operational modification of the original procedure described by Molander,[32] consisting of the use of a more concentrated (0.5 vs 0.1 M) solution of SmI_2 at

(24) For some non-Pauson–Khand enantioselective cycloaddition routes leading to five-membered rings, see: (a) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525–5528. (b) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752–4753. (c) Taber, D. F.; Amedio, J. C.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984–2990. (d) Yamamoto, A.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 375–378. (e) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837. For some enantioselective cyclization routes to five-membered rings, see: (f) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699–4702. (g) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935–5937. (h) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196–199. (i) Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 5927–5930. (j) Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821–1830. (k) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455–6456. (l) Nishida, M.; Hayashi, H.; Yamura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1995**, *36*, 269–272. (m) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S.-I. *Synlett* **1996**, 85–86. (n) Bertrand, M. P.; Crich, D.; Nouguier, R.; Samy, R.; Stien, D. *J. Org. Chem.* **1996**, *61*, 3588–3589. (o) Barnhart, R. W.; McMorran, D. A.; Bosnich, B. *J. Chem. Soc., Chem. Commun.* **1997**, 589–590. (p) Oppolzer, W.; Kuo, D. L.; Hutzinger, M. W.; Léger, R.; Durand, J.-O.; Leslie, C. *Tetrahedron Lett.* **1997**, *38*, 6213–6216.

(25) (a) Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357–360. (b) Dols, P. P. M. A.; Verstappen, M. M. H.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1993**, *49*, 11353–11372. (c) Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515–8538.

(26) For general surveys, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806.

(27) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251–4254.

(28) Cf.: Lipschutz, B. H.; Ellsworth, E. L.; Siahaan, I. J.; Shirazi, A. *Tetrahedron Lett.* **1988**, *29*, 6677.

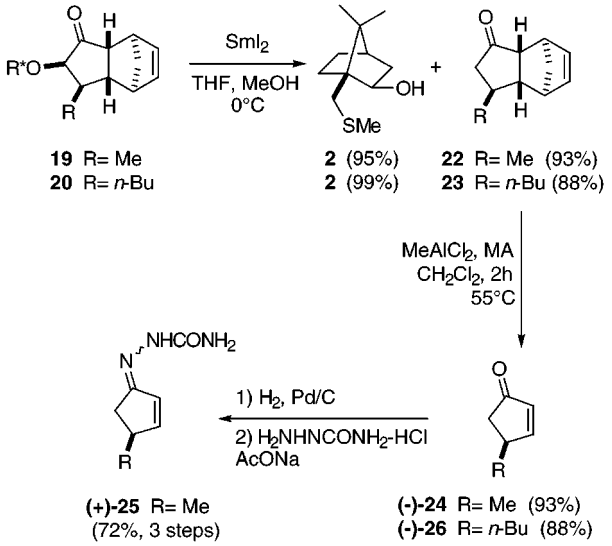
(29) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019–6022.

(30) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549–2550.

(31) Best results were obtained with samarium diiodide prepared in situ by Kende's method: Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699–1702.

(32) Molander, G. A.; Hahn, G.; *J. Org. Chem.* **1986**, *51*, 1135–1138.

Scheme 8



a much higher temperature (0 vs −78 °C) under argon, was used. This resulted in the rapid cleavage of the carbon−oxygen single bond (10 min) and gave rise to cyclopentanones **22** and **23** in excellent yields and allowed the recovery of auxiliary **2** in almost quantitative yield. Finally, among the existing methodologies to accomplish the last step in the sequence, we chose to explore the Lewis acid-catalyzed retro Diels−Alder conditions reported by Grieco,[33] which allow the reaction to be performed at low temperature. Thus, when the tricyclic ketones **22** and **23** were submitted to reaction with 1 equiv of $MeAlCl_2$ in the presence of maleic anhydride at 55 °C, they smoothly led in high yield to (−)-(*S*)-4-methyl-2-cyclopentenone (**24**) and (−)-(*S*)-4-butyl-2-cyclopentenone (**26**), respectively. Due to its volatility, cyclopentenone **24** (R = Me) was best isolated as the known (+)-(*R*)-3-methylcyclopentanone semicarbazone **25**.[34] The enantiomeric purity of **25**, determined by comparison of its optical rotation with that of an enantiomerically pure sample,[35] turned out to be 93%. This suggested that some racemization might have occurred, most likely in the final cycloreversion step. However, when dioxolane **27** derived from (−)-2,3-butanediol was prepared starting from optically active **26**, its ^{13}C NMR spectrum showed no peaks of the corresponding minor diastereomer.[36] This more solid evidence indicated that no significant racemization takes place in the retro Diels−Alder reaction and that the optical purity of the final 4-alkyl-2-cyclopentenones obtained according to the present synthetic scheme is ≥98% ee.

Rationalization of the Observed Diastereoselectivity. Although the mechanism of the Pauson−Khand reaction has not been studied in detail, the pathway

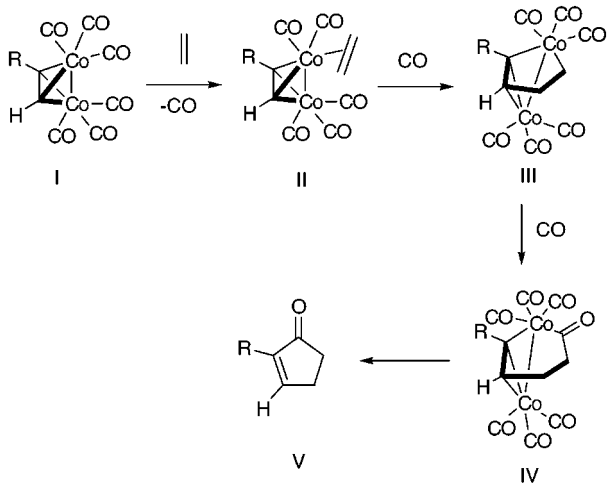


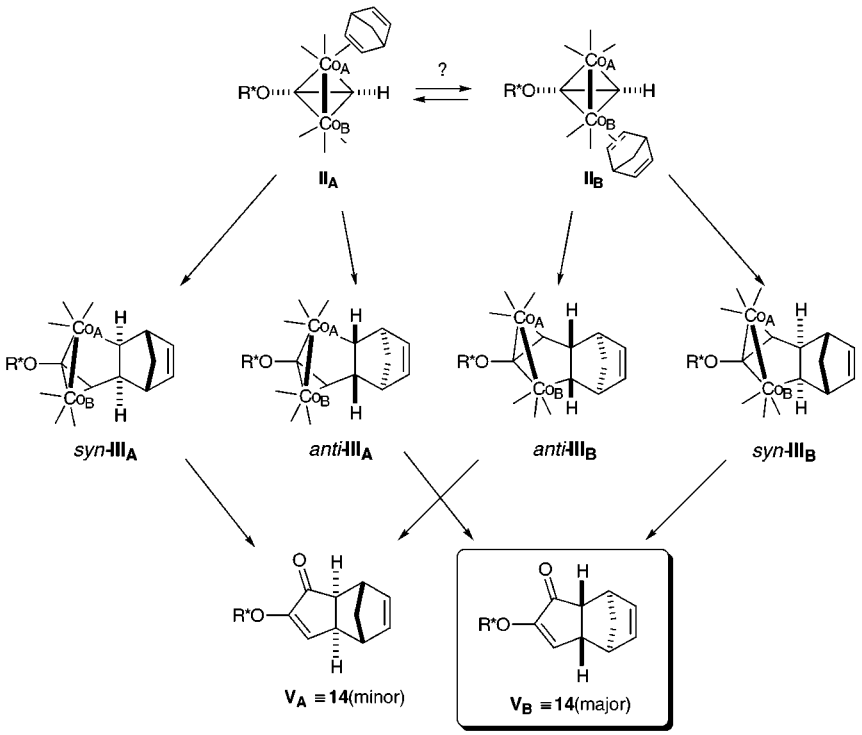
Figure 4. Commonly accepted mechanism of the Pauson−Khand reaction.

proposed by Magnus [37] (Figure 4), which accommodates the main experimental observations on the reaction, has found general acceptation. According to this proposal, the reaction involves four main steps from the initial complex **I**: (a) coordination of the reacting olefin to cobalt to give complex **II**, (b) insertion of the π-complexed olefin into a Co−C bond leading to cobaltacycle **III**, (c) insertion of carbon monoxide into the Co−C(sp^3) bond with formation of acylcobaltacycle **IV**, and (d) reductive elimination and loss of a dicobalt hexacarbonyl fragment to give the final cyclopentenone **V**.

Within the conceptual frame of this mechanism, the initial interaction between the dicobalt hexacarbonyl complex of a chiral alkoxyacetylene and a prochiral alkene, such as norbornadiene, can take place distinctly at either of the diastereotopic cobalt atoms (*pro-R* ≡ Co_A; *pro-S* ≡ Co_B) in the C_2Co_2 cluster; this will produce the diastereomeric complexes $\mathbf{II_A}$ and $\mathbf{II_B}$ (Scheme 9) in which, according to previous experience[3e] and to our experimental results, attack on the exo face of the olefin is assumed. Evolution of these complexes into the experimentally observed α-alkoxysubstituted cyclopentenone regioisomers can only take place through cobaltacycles **III**.[38] Up to four of these cobaltacycles can form depending both on the cobalt atom (Co_A, series **A**, or Co_B, series **B**) involved in the process and on the relative stereochemistry (syn or anti) of the methano bridge and the non-ring-forming $Co(CO)_3$ moiety. These cobaltacycles should then evolve in a pairwise manner into the diastereomers of the cyclopentenone adduct. Thus, whereas *syn*-$\mathbf{III_A}$ and *anti*-$\mathbf{III_B}$ would be transformed into $\mathbf{V_A}$, whose structure and stereochemistry are those of **14**(minor) when the R*OH ≡ **1**, *syn*-$\mathbf{III_B}$ and *anti*-$\mathbf{III_A}$ would lead to $\mathbf{V_B}$, which analogously corresponds to **14**(major). According to this, stereoselectivity can arise in the reactions as the result of different situations. Thus, two pathways could lead to the observed stereoi-

(33) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008−6010.
(34) Kokke, W. C. M.; Varkevisser, F. A. *J. Org. Chem.* **1974**, *39*, 1535−1539.
(35) Given the existence of *E*/*Z* isomers in **25**, which could influence the value of the optical rotation (cf. ref 34), a commercial sample of enantiomerically pure (*R*)-(+)-3-methylcyclopentanone (Aldrich, no. M3,970-9) was converted to the semicarbazone under exactly the same experimental conditions. This semicarbazone was subsequently used as a reference.
(36) The diastereomeric mixture of dioxolanes prepared from racemic 3-butylcyclopentanone and (−)-2,3-butanediol shows a well-resolved ^{13}C NMR spectrum. For the original method, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183-2186.
(37) (a) Magnus, P. C.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861−5859. (b) Magnus, P. C.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854. (c) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 6541−6556.
(38) The formation of these cobaltacycles has the stereoelectronic requirement of eclipsing C=C and Co−C(H) bonds. A similar set of regioisomeric cobaltacyles leading to the never detected β-alkoxy-substituted cyclopentenones would form via eclipsing of the C=C and the Co−C(OR*) bonds.

Scheme 9



somer **Vb** ≡ **14**(major): Coordination of the olefin to the *pro-R* cobalt atom leading to complex $\mathbf{II_A}$ and formation of the *anti*-cobaltacycle *anti*-$\mathbf{III_A}$ or, alternatively, coordination to the *pro-S* cobalt atom ($\mathbf{II_B}$) and formation of the syn cobaltacycle *syn*-$\mathbf{III_B}$.

In order to achieve a better understanding of the stereochemical outcome of the reaction of **10** with norbornadiene and other strained olefines, we wanted to answer three fundamental questions implicit in the mechanistic picture above:

(a) Does the chelating arm present in the chiral auxiliary efficiently discriminate between the diastereotopic cobalt atoms in the formation of the internally chelated species **10b**?

(b) Does a chelated complex preferentially react with an olefin through the cobalt atom involved in the chelation?

(c) Is there any preference for syn or anti stereochemistry in the putative cobaltacycle intermediates **III**?

To answer these questions, we decided to study the different intermediates involved in the reaction of **10** with norbornadiene by computational means. The geometries of all the studied species were fully optimized with the semiempirical procedure PM3(tm), which incorporates parametrization for transition metals to the original PM3 procedure,[39] as implemented in the package of programs SPARTAN 4.1.1,[40] after testing its performance in the description of dicobalt hexacarbonyl complexes of acetylenes.[41] To compare different reaction options, accurate energies were subsequently evaluated by single point calculations performed with density functional theory (DFT), as implemented in the ADF 2.0.1 code,[42] using the VWN local exchange correlation potential[43] with Perdew−Wang 91 nonlocal exchange and correlation corrections.[44]

(a) Structure and Configurational Stability of the Chelated Complex 10b. As we have seen in the preceding sections, the use in Pauson−Khand reactions of acetylenic ethers derived from auxiliaries **1**−**3** introduces a new element in the mechanistic pathway: the generation of internally chelated complexes. In fact, the generation of these complexes (**10b**−**12b**) is crucial to the achievement of diastereoselectivity, so that it is important to know their structures and configurational stability. In principle, the (methylthio)methyl arm can occupy either the axial or one of the equatorial coordination sites (the other one is not available due to geometrical reasons) at either of the two cobalt atoms. All four possible structures were located and minimized with the theoretical procedure discussed above. For each of the complexes, two structures of very similar energy, differing only in the orientation of the methyl substituent, were located; only the most stable ones have been considered. The most stable complex ($\mathbf{I_A}$-**ax**) involves the coordination of the (methylthio)methyl arm at the axial site of the *pro-R* cobalt atom. The preference of phosphine-[45] and

(39) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220.

(40) SPARTAN, version 4.1.1, Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA, 92612.

(41) PM3(tm) reproduces well the structure and conformation of dicobalt hexacarbonyl complexes of alkynes as determined by X-ray crystallography. With respect to the C_2Co_2 cluster, both the Co−Co and the C−Co distances are accurately reproduced, while the C−C distance is somewhat overestimated. If desired, this parameter can be fixed to the mean crystallographic value of 1.336 Å without introduction of distortion in the overall structure. With respect to coordinatively unsaturated cobalt species, PM3(tm) shows an exaggerated tendency (with respect to higher level DFT methods) to saturate cobalt either through bridging carbonyls or through agostic interactions with hydrogen atoms. Structures presenting these characteristics should be treated carefully until confirmation of these effects by means of independent DFT optimization.

(42) (a) Baerends, E. J.; Ellis, D. E.; Ros, P. E. *Chem. Phys.* **1973**, *2*, 41−51. (b) Versluis, L.; Ziegler, T. *J. Chem. Phys.* **1988**, *88*, 322−328. (c) Fan, L.; Ziegler, T. *J. Chem. Phys.* **1991**, *95*, 7401−7408. (d) teVelde, G.; Baerends, E. J. *J. Comput. Phys.* **1992**, *99*, 84−98.

(43) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211.

(44) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev. B* **1992**, *46*, 6671−6687.

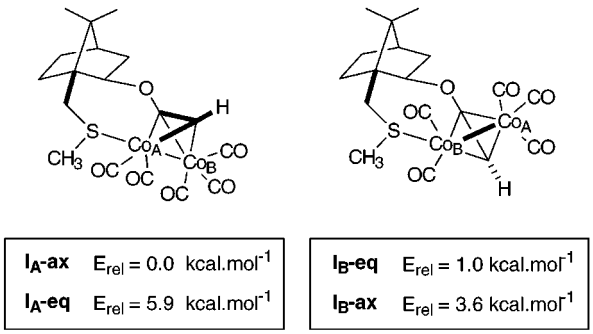


Figure 5. DFT calculated relative energies of the internally chelated pentacarbonyl complexes **I**.

thioether-type[46] ligands for axial positions in cobalt carbonyl complexes of alkynes is well documented. However, the cyclic nature of **10b** could somewhat affect the normal pattern of stabilities,[47] as shown by the fact that the next most stable complex ($\mathbf{I_B}$-**eq**) involves substitution at an equatorial site of the *pro-S* cobalt. The DFT-calculated relative energies of the located minima are shown in Figure 5, whereas the PM3(tm)-optimized structures of the most stable complexes ($\mathbf{I_A}$-**ax** and $\mathbf{I_B}$-**eq**) are in Figure 6 (left). Thus, the performed theoretical calculations predict that **10b** will largely (≥85%) exist at room temperature as a single diastereomer (represented by $\mathbf{I_A}$-**ax**) with the *pro-R* cobalt coordinated to sulfur. This is compatible with the NMR results discussed earlier.

An important concern that arises when the diastereoselectivity of the Pauson−Khand reactions of **10b** is considered is the configurational stability of the chelate. It is known from NMR studies at variable temperature that the dicobalt hexacarbonyl complexes of alkynes are fluxional at ordinary temperatures.[48] However, it is believed that this fluxionality is due to carbonyl motions at a single cobalt atom. In this respect, it is important to recall that some diastereomerically pure phosphine-substituted cobalt carbonyl complexes of alkynes show good configurational stability at room and even higher temperatures.[6a−c,45c]

In any case, the viability of a low-energy epimerization pathway for **10b**, as represented in Scheme 10, was investigated. A structure with the characteristics of $\mathbf{I_{bridge}}$ was shown to be an energy minimum at the PM3(tm) level of theory. Then, a single-point DFT calculation[49] provided for $\mathbf{I_{bridge}}$ a relative energy of +20.2 kcal·mol^{-1} (respect to $\mathbf{I_A}$-**ax**). Since $\mathbf{I_{bridge}}$ should be connected with the chelated species through a higher energy transition state, the present theoretical results tend to indicate that complexes such as $\mathbf{I_A}$-**ax** will be configurationally stable over the range of temperatures in which the Pauson−Khand reactions of **10b** take place with useful diastereoselectivity.[50]

(b) Coordination of Norbornadiene to Cobalt: Structure of the π-Complexes II. Once the chelated complex **I** is formed, and its interaction with the reacting olefin [norbornadiene as a typical example] is allowed to take place, the initial stage of the Pauson−Khand reaction could in principle occur according to routes **a** or **b**, as represented in Scheme 11. In route **a**, the olefin would coordinate to the nonchelated cobalt atom, whereas in route **b** coordination of the olefin would occur at the site formerly occupied by sulfur.

Although a route similar to **a** could be operating in the Pauson−Khand reactions of phosphine-substituted cobalt carbonyl complexes,[6] the lability of the cobalt−sulfur bond, predicted by model PM3(tm) calculations,[51] suggests that route **b** could be operating in this case. This assumption, analogous to Krafft's mechanistic hypothesis for the intramolecular Pauson−Khand reactions accelerated by coordinating ligands,[8d,e] provides a rationale for understanding the greatly increased reactivity of **10b** relative to **10a**.[52] Accordingly, only route **b** has been explored in the present theoretical study.

In a solvent with coordinating ability like dichloromethane, in which the reactions are performed, it is logical to expect that solvent molecules will contribute to stabilize the coordinatively unsaturated intermediate generated in the dissociative step, thus lowering its energy barrier.[53] We have represented in Scheme 12 the plausible course of the ligand-substitution process. The effect of solvent has been taken into account by means of a single dichloromethane molecule.

For simplicity, we have represented and evaluated the substitution process as taking place at a single coordination site (axial, *pro-R* cobalt), although this is not necessarily the case. The important finding, which is rather independent of this assumption, is that *ligand substitution on* $\mathbf{I_A}$-**ax** *leading to the first intermediate in the Pauson−Khand reaction* $\mathbf{II_A}$-**ax** *is predicted to be an essentially thermoneutral process with low activation energy when the presence of a coordinating solvent is included in the calculation*.[54] For comparison, when the molecule of dichoromethane is not included in the calculation, the cleavage of the sulfur−cobalt bond in $\mathbf{I_A}$-**ax** is calculated to be endothermic by 33.8 kcal·mol^{-1}.

(45) See, for instance: (a) Bonnet, J.-J.; Mathieu, R. *Inorg. Chem.* **1978**, *17*, 1973−1976. (b) Arewgoda, M.; Robinson, B. H.; Simpson, J. *J. Am. Chem. Soc.* **1983**, *105*, 1893−1903. (c) Bradley, D. H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1989**, *8*, 554−556. (d) Jeffery, J. C.; Pereira, R. M. S.; Vargas, M. D.; Went, M. J. *J. Chem. Soc., Dalton Trans.* **1995**, 1805−1811.

(46) Rumin, R.; Manojlovic-Muir, L.; Muir, K. W.; Pétillon, F. Y. *Organometallics* **1988**, *7*, 375−383.

(47) For an example of a complex bis-equatorially substituted by DPPM, see: Gelling, A.; Went, M. J.; Povey, D. C. *J. Organomet. Chem.* **1993**, *455*, 203−210.

(48) (a) Aime, S.; Milone, L.; Rossetti, R.; Stanghellini, P. L. *Inorg. Chim. Acta* **1977**, *22*, 135−139. (b) Band, E.; Muetterties, E. L. *Chem. Rev.* **1978**, *78*, 639−658.

(49) A geometry optimization of I_{bridge}, performed at the same DFT level used for energy calculations in the present study, showed that the bridged structure is a stationary point at that level of theory.

(50) Note, however, that this or a similar mechanism could be involved in a hypothetical equilibration of **10b** when generated at room temperature by NMO oxidation of **10a** in the absence of any olefin. Under these reaction conditions (presence of olefin), if diastereoselectivity depends on cobalt-specificity of the chelating arm/olefin substitution process, its level will be determined by the relative rates of Pauson−Khand reaction and epimerization. This is in agreement with the fact that the more reactive olefins provide the higher diastereomeric ratios of ketone products.

(51) A systematic PM3(tm) study of bond dissociation energies on (acetylene)$Co_2(CO)_5(SMe_2)$ reveals that the cobalt−sulfur bond is the weakest in the molecule by ∼4 kcal·mol^{-1}.

(52) Phosphine-substituted dicobalt pentacarbonyl complexes of alkynes are less reactive toward alkenes than the parent hexacarbonyl complexes. See, for instance, ref 6e and: Bradley, D. H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1992**, *11*, 2598−2607.

(53) For a similar suggestion on solvent stabilization of (otherwise) unsaturated intermediates in ligand-exchange reactions taking place by a dissociative mechanism, see: Cowey, W. D.; Brown, T. L. *Inorg. Chem.* **1973**, *12*, 2820−2825.

(54) The enthalpy change of the first step (+15.1 kcal·mol^{-1}) should be similar to the activation enthalpy of the substitution process.

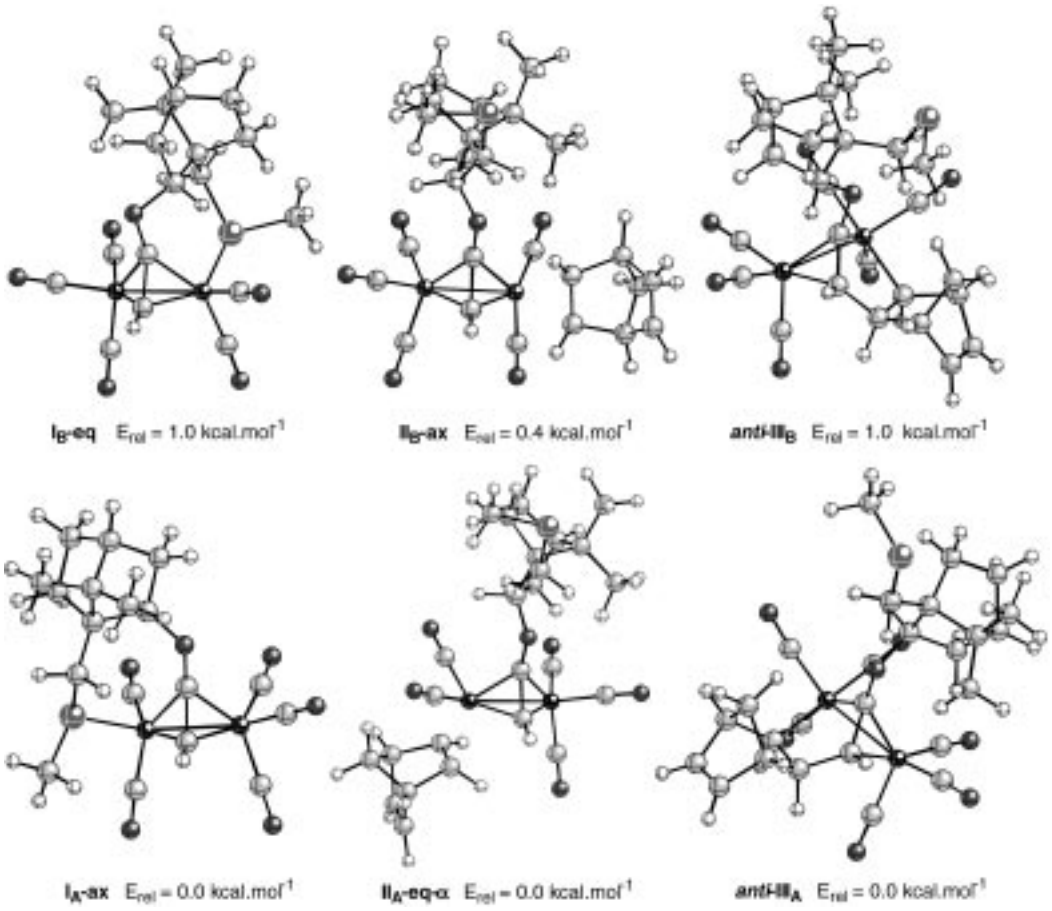
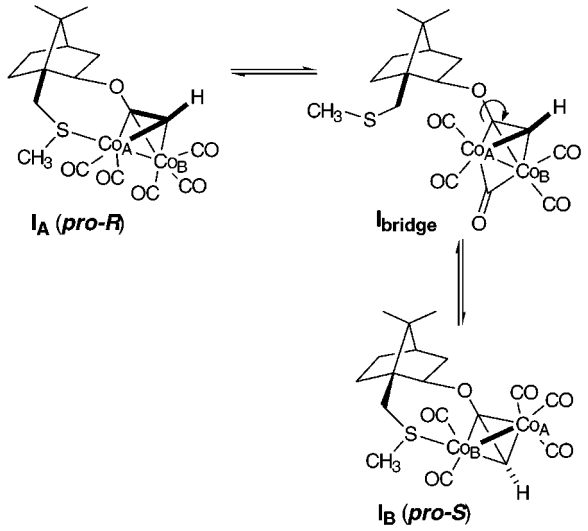


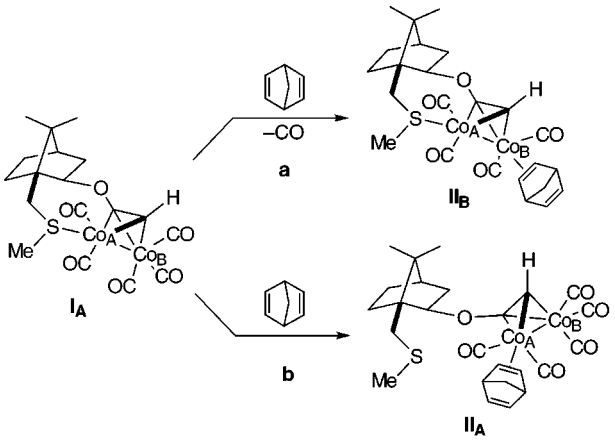
Figure 6. PM3(tm)-optimized structures and DFT-calculated relative energies of the most stable stereoisomers of intermediates **I** (left), **II** (middle), and **III** (right) leading to the major and minor diastereomers of **V**.

Scheme 10



Since we have previously shown that epimerization of $\mathbf{I_A}$ to $\mathbf{I_B}$ involves a rather high-energy pathway and because it is known that norbornadiene reacts only on its exo face, we next explored the existence of different energy minima of the π-olefin complexes **II** involving coordination of the exo face of norbornadiene to the *pro-R* cobalt atom in the C_2Co_2 cluster. Due to previous knowledge on fluxionality of similar complexes,[48a] no site specificity (i.e., axial/axial or equatorial/equatorial) was considered for the substitution process.

Scheme 11



In addition, to allow comparison with the nonselective, purely thermal reactions of **10a**, which should probably take place through both cobalt atoms, we also studied the set of complexes **II** containing an exo-coordinated norbornadiene unit at the different sites of the *pro-S* cobalt atom. The DFT-calculated relative energies of the most stable conformational minima located for the three possible coordination sites of the *pro-R* cobalt ($\mathbf{II_A}$) and of the *pro-S* cobalt atom ($\mathbf{II_B}$) are shown in Figure 7.

As we have already mentioned, the stereoelectronic requirement for the evolution of these complexes to cobaltacycles en route to cyclopentenones is a synperiplanar arrangement of the C=C and the Co−C bonds participating in the metathesis step.[3e] Accordingly,

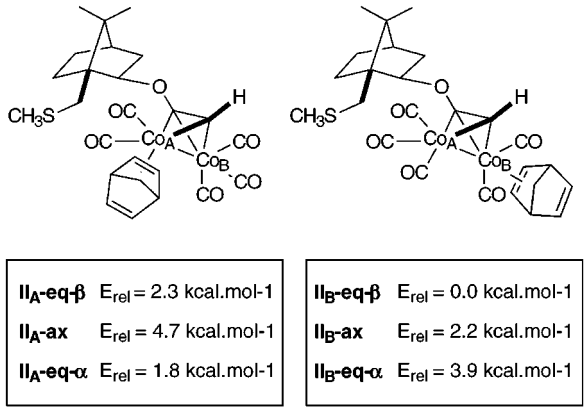
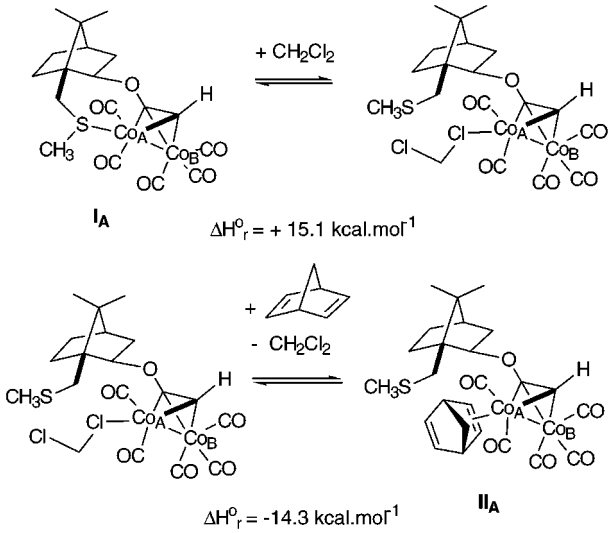


Figure 7. DFT-calculated relative energies of the norbornadiene π-complexes **II**.

Scheme 12



complexes **II_A-eq**-β and **II_B-eq**-β could only lead to a β-alkoxy-substituted cyclopentenone, which is never observed, and, thus, does not require further consideration. On the other hand, each of the other four complexes could in principle lead to either of the two possible diastereomers of **V**, depending on the stereochemistry (syn or anti) of the intermediate cobaltacycle (see Scheme 9). It is worth noting that, among the olefin complexes able to lead to the observed products, the most stable one is **II_A-eq**-α, in which the alkene is coordinated to the same cobalt atom (Co_A) that is involved in the most stable pentacarbonyl complex **I_A**. The PM3(tm)-optimized structures of the most stable π-complexes at each cobalt atom (**II_A-eq**-α and **II_B-ax**) are shown in Figure 6 (middle).

(c) Structure of the Cobaltacycles III and Origin of the Observed Stereoselectivity. At this point of the discussion, it is necessary to analyze the preferred stereochemistry and relative energies of the four possible cobaltacycles **III** leading to the observed final products. While it is not clear whether the formation of these species takes place in a concerted or stepwise manner, it can be anticipated that the addition of CO (or a coordinating solvent) to a hypothetical, coordinatively unsaturated (16-electron) intermediate cobaltacycle should take place without (or with very low) activation energy. We have represented in Figure 8 the DFT-calculated relative energies of the four possible cobaltacycles **III**, while the

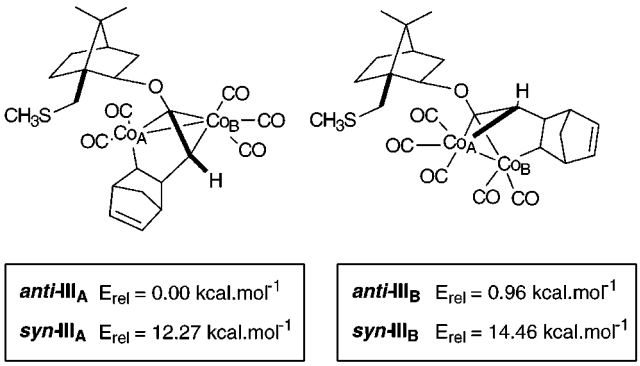
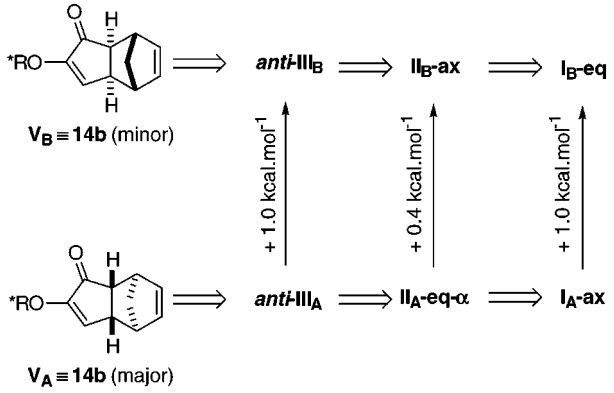


Figure 8. DFT-calculated relative energies of the cobaltacycles **III**.

Scheme 13



PM3 structures of the most stable anti-type cobaltacycles are shown in Figure 6 (right).

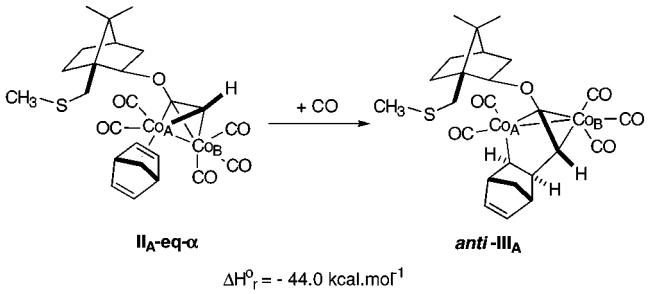
The first important point relative to these structures that deserves comment is the great difference in stability between the syn and anti cobaltacycles. If we admit that the transition states leading to these structures should reflect their energy differences, it follows as a consequence that syn cobaltacycles are not intermediates in the Pauson−Khand reactions of **10b** with olefins containing the bicyclo[2.2.1]heptane skeleton. Then, *the sole factor determining the diastereoselectivity of the process is the cobalt atom in the C_2Co_2 cluster participating in the formation of the cobaltacycle.*

The clear energetic preference for anti-type cobaltacycles (*anti*-**III**), together with the predicted configurational stability of intermediates **I** and **II**, allows the establishment of a genealogy for the diastereomers of the reaction product **V**, back to the chelated complexes **I** (Scheme 13).

Thus, the major stereoisomer of **14** (represented by **V_A**) can only arise from cobaltacycle *anti*-**III_A**, in which all the stereochemical information is already present. This cobaltacycle, in turn, can only arise from the olefin complex **II_A-eq**-α, while **II_A-eq**-α would likewise arise from the most stable chelated complex with the (methylthio)methyl arm located at the *pro-R* cobalt, i.e., **I_A**. Analogous arguments allow the tracing of the origin of the minor estereoisomer of **14** (represented by **V_B**) back to the most stable of the chelated complexes with the sulfur side chain on the *pro-S* cobalt (**I_B-eq**). *Very interestingly, the present calculations predict that the major stereoisomer of the cyclopentenone adduct is formed through the sequence with the most stable intermediates.*

Two additional aspects of these sequences deserve

Scheme 14



comment. First, it has been generally assumed that cobaltacycle formation is the product-determining step in the Pauson−Khand reaction. If one looks at the energetics of this process in one particular case, i.e., the conversion of $\mathbf{II_A}$-**eq**-α into *anti*-$\mathbf{III_A}$, as shown in Scheme 14, the calculated strong exothermic character indicates that this step will be irreversible in practice, thus confirming the qualitative predictions.

The second aspect refers to the stabilities of the olefin complexes ($\mathbf{II_A}$/$\mathbf{II_B}$) (Figure 6). When these complexes arise from the equilibrium mixture of chelated complexes ($\mathbf{I_A}$/$\mathbf{I_B}$), generated either thermally or, preferentially, oxidatively but always in the absence of the olefin component (as we have considered until now), a clear predominance of $\mathbf{II_A}$, with the olefin located at the (formerly) *pro-R* cobalt is to be expected. Conversely, when the reaction is performed with thermal activation and with the olefin present from the first moment, the intermediacy of a chelated complex is not necessarily involved, and the participation in the process of the set of complexes $\mathbf{II_B}$ could be enhanced. As a consequence, a decrease in diastereoselectivity should be expected; this is exactly what is experimentally observed (Table 2).

In summary, although a complete mechanistic picture of the Pauson−Khand reaction is still far away, the DFT//PM3(tm) calculations performed on the different intermediates in the reaction of **10b** with norbornadiene provide answers for the main questions underlying the stereochemical outcome of the process and allow the rationalization of the observed diastereoselectivity: The formation of a chelated complex directs the reaction toward a precise cobalt atom (the *pro-R* one in the initial complex). A subsequent ligand substitution process (sulfide/olefin) at that cobalt atom leads to an intermediate $\mathbf{II_A}$ already containing all of the structural elements of the final product, and the irreversible evolution of this intermediate into an anti cobaltacycle anti-$\mathbf{III_A}$ creates the new stereogenic centers with the configuration found in the major diastereomer of the final product.

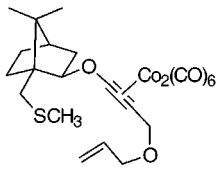
Concluding Remarks

The chiral auxiliaries with chelating ability represent a new useful concept for diastereocontrol in Pauson−Khand reactions. The oxidation with NMO of the dicobalt hexacarbonyl complexes of the alkoxyacetylenes derived from these auxiliaries selectively leads to pentacarbonyl complexes, whose stabilization can be attributed to an effective dative bond between the alkylthio appendage in the auxiliary and the coordinatively unsaturated cobalt atom. Spectroscopic data and theoretical calculations are consistent with the predominance of a single diastereomer in these chelated complexes, thus indicating that the chiral information contained in the auxiliary has been effectively transmitted to cobalt. Both the observed diastereoselectivities in the low-temperature Pauson−Khand reactions of the chelated complexes and the results of the theoretical study indicate that, at low temperature, substitution of the alkylthio ligand by a reacting olefin occurs with cobalt specificity. Given the predicted high energetic preference for anti-type cobaltacycles, reaction (olefin coordination and irreversible cobaltacycle formation) at a single cobalt atom is a sufficient condition for stereocontrol. In this way, the chiral information is transmitted from cobalt to the final reaction product.

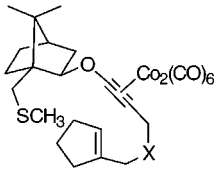
From an operational point of view, *a unique advantage offered by the present methodology is the possibility of performing the normally difficult first dissociative step of the Pauson−Khand reaction in a facile and stereocontrolled manner and in the absence of a reacting olefin*. The so-formed reactive species can then be brought to the desired temperature for reaction. From a practical perspective, the Pauson−Khand reaction of alkoxyacetylenes derived from chelating auxiliaries has already found application as the key step in a highly enantioselective synthesis of (+)-brefeldin A.[7a]

If these auxiliaries had to be used in *intramolecular* Pauson−Khand reactions, the generation of the internally chelated species in the absence of a reacting olefin would be no longer possible. According to our arguments, the achievement of stereocontrol in such reactions should greatly depend on the relative rates of the generation (and, probably, equilibration) of the chelated intermediate and of the subsequent Pauson−Khand reaction. This is, in fact, what is experimentally observed. Thus, when the cobalt complex **28** is submitted to either thermal or chemical (NMO) activation, the formation of an intermediate complex cannot be observed by TLC, and the Pauson−Khand adduct is formed with low diastereoselectivity (≤2:1).[7b] Conversely, in the case of complexes **29**−**31**, the formation of chelated pentacarbonyl complexes is readily promoted either thermally or chemically, as evidenced by TLC, and the subsequent evolution of these complexes into cyclopentenone adducts takes place with high diastereoselectivity (up to 12:1).[7b,d]

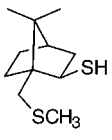
The concepts that led to the synthesis and use of **1**−**3** have also fostered the preparation of the thiol analogue **32**.[55] Quite gratifyingly, the Pauson−Khand chemistry of **32** follows the same pattern as with **1**−**3**, and its cycloaddition with norbornadiene takes place with diastereoselectivities of up to 95:5.[56]



28



29 X = O
30 X = CH_2
31 X = $C(CH_3)_2$



32

We are currently exploring new aspects and applications of the chemistry of coordinatively modified cobalt

(55) Montenegro, E.; Echarri, R.; Claver, C.; Castillón, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3553−3558.

(56) Montenegro, E.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1998**, *39*, 335−338.

carbonyl complexes of alkynes. Results will be reported in due course.

Experimental Section

Computational Details. Geometry optimizations at the PM3(tm) level of theory were performed without geometrical restrictions. For DFT calculations, a double-ζ STO basis set was used. The frozen core approximation[42a] was used for the $1s^2$ shell on carbon and oxygen, as well as the $1s^2$, $2s^2$, and $2p^6$ shells on cobalt, chlorine, and sulfur.

General Methods. Melting points were determined in a open capillary tubes and are uncorrected. Infrared spectra were recorded in Fourier transform mode, using film (NaCl) or KBr pellet techniques. The ^{1}H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ unless specified otherwise, with tetramethylsilane as internal standard. The ^{13}C NMR spectra were recorded at 50.3 or 75.4 MHz in $CDCl_3$ unless specified otherwise. Signal multiplicities were established by DEPT experiments. In all cases, chemical shifts are in ppm downfield of TMS. Mass spectra were recorded at 70 eV ionizing voltage; ammonia was used for chemical ionization (CI). Elemental analyses were performed by the Servei d'Anàlisis Elementals del CSIC de Barcelona, and exact mass measurements (HRMS) were performed by the Laboratori d'Espectrometria de Masses del CSIC de Barcelona. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. Hexamethyl phosphoramide (HMPA) was purified by distillation from CaH_2 at reduced pressure and stored over 4 Å molecular sieves. All reactions were performed in flame- or oven-dried glassware under an N_2 or Ar atmosphere. Reaction progress was followed by TLC (silica gel 60, F254). Silica gel (70−230 mesh) was used for column chromatography. (2*R*)-10-Mercaptoisoborneol (**4**),[15] 10-iodocamphor (**5**),[17] and (2*R*)-10-(methylthio)isoborneol (**1**)[16] were prepared by literature procedures.

(2*R*)-10-(Neopentylthio)isoborneol (2). In a round-bottomed flask under N_2, sodium hydride (90 mg, 3.0 mmol, 80% in oil) was washed twice with anhydrous hexane (2 mL). In this order, anhydrous THF (3 mL) and a solution of 10-mercaptoisoborneol (0.5 g, 2.7 mmol) in THF were added via syringe. The resulting slurry was stirred at room temperature for 30 min. Then, neopentyl bromide (210 μL, 3.0 mmol) and HMPA (2 mL) were added via syringe. The reaction mixture was heated at reflux overnight. The reaction was cautiously quenched with water, the aqueous layer was extracted with ether, and the combined organic layers washed with brine and dried ($MgSO_4$). Solvent removal under vacuum afforded a mixture of 10-(neopentylthio)isoborneol and starting material. Further purification by column chromatography (SiO_2, hexane/AcOEt, 2%) yielded 350 mg of **2** (70% yield) as a colorless oil: $[\alpha]_D = -50.1$ (*c* 1.6, $CHCl_3$); IR (film) $\nu_{max} = 3470$ (broad), 2950, 1475, 1390, 1365, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.99 (s, 9H), 1.05 (s, 3H), 0.93−1.11 (m, 1H), 1.19−1.32 (m, 1H), 1.47−1.58 (m, 1H), 1.63−1.85 (m, 4H), 2.17 (s broad, 1H), 2.44−2.54 (AB, J = 12 Hz, 2H), 2.51−2.80 (AB, J = 10 Hz, 2H), 3.88−3.92 (dd, J = 3 and 8 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3 (CH_3), 21.1 (CH_3), 27.6 (CH_2), 29.4 ($3CH_3$), 31.6 (CH_2), 33.9 (C), 34.9 (CH_2), 39.4 (CH_2), 45.6 (CH), 48.0 (C), 49.5 (CH_2), 52.9 (C), 77.6 (CH) ppm. Anal. Calcd for $C_{15}H_{28}OS$: C, 70.25; H, 11.00; S, 12.50. Found: C, 70.20; H, 11.11; S, 12.24.

(+)-10-(Phenylthio)camphor (6). In a round-bottomed flask under N_2, sodium hydride (120 mg, 4.0 mmol, 80% in oil) was washed twice with anhydrous hexane (2 mL). THF (2 mL) was added via syringe and the flask cooled at 0 °C. Next, thiophenol (350 μL, 3.4 mmol) was added neat via syringe, and the reaction mixture was stirred at room temperature for 30 min. To this slurry, a solution of 10-iodocamphor (**5**)[17] (0.8 g, 2.8 mmol) in THF (2 mL) and HMPA (1.5 mL) were added via syringe. The reaction mixture was heated at reflux, and the progress of the reaction was monitored by TLC. After complete consumption of the starting material (2−4 h), the reaction was cautiously quenched with water and the aqueous layer extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography (SiO_2, hexane/AcOEt, 2.5%) of the residue afforded 160 mg (87% yield) of 10-(phenylthio)camphor as a colorless oil: $[\alpha]_D = +7.0$ (*c* 1.5, $CHCl_3$); IR (film) $\nu_{max} = 2960$, 1740, 1585, 1480, 1050 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.09 (s, 3H), 1.15−1.61 (m, 2H), 1.75−2.23 (m, 4H), 2.34−2.50 (m, 1H), 2.88−3.37 (AB, J = 11 Hz, 2H), 7.10−7.45 (m, 5H) ppm; ^{13}C NMR (50 MHZ, $CDCl_3$) δ 20.1 (CH_3), 20.3 (CH_3), 26.5(CH_2), 26.9 (CH_2), 30.8 (CH_2), 43.0 (CH_2), 43.4 (CH), 47.8 (C), 60.8 (C), 125.6 (CH), 128.5 (CH), 128.8 (CH), 138.2 (C) ppm; HRMS (EI) calcd for $C_{16}H_{20}OS$ 260.1235, found 260.1233.

(2*R*)-10-(Phenylthio)isoborneol (3). In a round-bottomed flask under N_2 were placed $LiAlH_4$ (26 mg, 0.68 mmol) and ether (1 mL). The resulting slurry was cooled at 0 °C, and a solution of 10-(phenylthio)camphor (**6**) (149 mg, 0.57 mmol) in ether (5 mL) was added dropwise via syringe. The mixture was stirred at room temperature for 2 h, and the reaction was quenched by sequential addition of 26 μL of water, 26 μL of 15% NaOH, and 80 μL of water. The resulting white precipitate was filtered through Celite and washed with ether. The filtrate was dried ($MgSO_4$) and concentrated in vacuo to provide a mixture of exo/endo isomers in a 10/1 ratio (^{1}H NMR). The exo isomer was purified by flash column chromatography (SiO_2, hexane/AcOEt, 2%) to afford 127 mg (85% yield) of 10-(phenylthio)isoborneol as a colorless oil: $[\alpha]_D = -35.5$ (*c* 2.8, $CHCl_3$); IR (film) ν_{max}= 3450 (broad), 2940, 1585, 1485, 1070 cm^{-1}: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.09 (s, 3H), 1.00−1.90 (m, 7H), 2.95−3.23 (AB, J = 12 Hz, 2H), 3.89−3.99 (m, 1H), 7.15−7.50 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4 (CH_3), 21.7 (CH_3), 27.6 (CH_2), 31.5 (CH_2), 34.4 (CH_2), 39.7 (CH_2), 45.7 (CH), 48.3 (C), 52.7 (C), 77.3 (CH), 126.4 (CH), 129.4 (CH), 129.5 (CH), 137.9 (C) ppm; HRMS (EI) calcd for $C_{16}H_{22}OS$ 262.1391, found 262.1388.

(2*R*-*exo*)-2-[(*E*)-Dichloroethenoxy]-10-(methylthio)bornane (7). In a round-bottomed flask under N_2, potassium hydride in mineral oil (35%, 2.4 g, 21 mmol) was washed with anhydrous hexane (3 × 10 mL). Anhydrous THF (2 mL) was added, and over the resulting slurry was added dropwise a solution of 10-(methylthio)isoborneol (**1**) (2.0 g, 10 mmol) in THF (20 mL) via cannula. After the hydrogen evolution ceased, the solution was cooled to −40 °C, and a solution of trichloroethene (1.37 g, 10.5 mmol) in THF (15 mL) was added via cannula. The reaction mixture was allowed to warm gradually at −10 °C. At this point, TLC analysis revealed complete conversion of the starting material. The reaction was carefully quenched with MeOH and poured over saturated NH_4Cl solution. The aqueous layer was extracted with hexane, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/AcOEt, 2.5%) afforded 2.3 g (78% yield) of *exo*-2-[(*E*)-dichloroethenoxy]-10-(methylthio)bornane as a colorless oil: $[\alpha]_D = -72.3$ (*c* 1.8, $CHCl_3$); IR (film) ν_{max}= 3120, 2970, 1665, 1285, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.12 (s, 3H), 1.00−2.10 (m, 7H), 2.14 (s, 3H), 2.50, 2.92 (AB, J = 12 Hz, 2H), 4.50 (dd, J = 3, 7 Hz, 1H), 5.41 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.4 (CH_3), 19.9 (CH_3), 20.4 (CH_2), 26.7 (CH_2), 30.7 (CH_2), 33.1 (CH_2), 38.0 (CH_2), 45.3 (CH), 47.8 (C), 53.2 (C), 85.6 (CH), 95.4 (CH), 142.5 (C) ppm. MS (DIP-CI−NH_3) *m/e* = 183 ($M^+ - C_2HCl_2O$, 100), 295 ($M^+ + 1$, 33), 312 ($M^+ + 18$, 67), 327 ($M^+ + 35$, 57).

(2*R*-*exo*)-2-[(*E*)-Dichloroethenoxy]-10-(neopentylthio)-bornane (8). This compound was prepared following the experimental procedure employed for the synthesis of **7**. *exo*-2-[(*E*)-Dichloroethenoxy]-10-(neopentylthio)bornane was obtained in 74% yield as a colorless oil: $[\alpha]_D = -51.7$ (*c* 1.3, $CHCl_3$); IR (film) $\nu_{max} = 3110$, 2970, 1670, 1630, 1280, 1080 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.97 (s, 9H), 1.11 (s, 3H), 1.00−2.05 (m, 7H), 2.47 (s, 2H), 2.50−2.88 (AB, J = 12 Hz, 2H), 4.49−4.58 (dd, J = 3, 7 Hz, 1H), 5.39 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0 (CH_3), 20.5 (CH_3), 26.8 (CH_2), 28.9 ($3CH_3$) 30.7 (CH_2), 32.9 (C), 33.0 (CH_2), 38.0 (CH_2), 45.5 (CH), 47.8 (C), 49.2 (CH_2), 52.7 (C), 85.5 (CH), 95.3 (CH), 143.0 (C) ppm.

(2*R*-*exo*)-2-[(*E*)-Dichloroethenoxy]-10-(phenylthio)bornane (9). The above compound was prepared following the experimental procedure employed for the synthesis of **7**. *exo*-2-[(*E*)-Dichloroethenoxy]-10-(phenylthio)bornane was obtained in 77% yield as a colorless oil: $[\alpha]_D = -76.6$ (*c* 1.6, $CHCl_3$); IR (film) $\nu_{max} = 2950, 1625, 1480, 1280\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.16 (s, 3H), 1.00−2.10 (m, 7H), 2.92−3.39 (AB, $J = 12$ Hz, 2H), 4.49−4.58 (dd, $J = 3, 7$ Hz, 1H), 5.36 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (CH_3), 20.5 (CH_3), 26.8 (CH_2), 30.7 (CH_2), 32.9 (CH_2), 38.1 (CH_2), 45.4 (CH), 48.2 (C), 52.9 (C), 85.4 (CH), 95.8 (CH), 125.6 (CH), 128.6 (CH), 129.2 (CH), 137.8 (C), 142.5 (C) ppm; HRMS (EI) calcd for $C_{18}H_{22}Cl_2OS$ 356.0768, found 356.0769.

General Procedure for the Preparation of the Hexacarbonyl-/PentacarbonylDicobalt Complexes: Dicobalt Complexes of (2*R*-*exo*)-2-(Ethynyloxy)-10-(methylthio)-bornane (10a/10b). To a solution of **7** (2.12 g, 7.8 mmol) in ether (20 mL) under nitrogen at −65 °C was added dropwise *n*-BuLi (10.4 mL, 16.3 mmol) via syringe. The reaction mixture was stirred for 30 min at −65 °C and then allowed to warm gradually to −10 °C; TMSCl (1.47 mL, 11.7 mmol) was added via syringe. A white solid formed, and the reaction mixture was stirred for 2 h at room temperature. At this point, IR analysis showed complete conversion to the corresponding silylated alkyne. Upon dilution with hexane, the crude was filtered through Celite and the solvent removed in vacuo. The residue was dissolved in hexane (50 mL), and solid $Co_2(CO)_8$ (90%, 3.2 g, 8.5 mmol) was added to this solution. When CO evolution ceased (15 min), the solvent was partially evaporated and the complex filtered through a short pad of alumina (hexane/AcOEt, 2%). Solvent removal yielded a red oily residue. The red complex was dissolved in MeOH (75 mL) under CO atmosphere and treated with K_2CO_3 (3.1 g) under vigorous stirring. After 30 min at room temperature, TLC analysis showed complete deprotection of the TMS group.[57] Methanol was then partially evaporated, and the solution was extracted with hexane. The hexane layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield 2.3 g of **10a** (62% overall yield) as a viscous red oil. On standing, **10a** slowly evolves into **10b** with loss of carbon monoxide. This evolution can be avoided by keeping **10a** under a CO atmosphere. When a hexane solution of **10a** was heated at 50 °C, a maximum concentration of **10b** (**10b**/**10a** ≈ 85/15) was achieved after 1 h. By treating a dichloromethane solution of **10a** with *N*-methylmorpholine *N*-oxide (ca. 6 equiv) at room temperature, a complete conversion to **10b** was observed. Except for the thermal or *N*-oxide-promoted conversion to **10b**, the hexacarbonyl complex **10a** was not manipulated before use in Pauson−Khand reactions. Hexacarbonyl complex **10a**: red spot on TLC ($R_f = 0.75$, SiO_2, hexanes/ethyl acetate 9/1); IR (film) $\nu_{max} = 2086, 2046, 2016, 1957\ cm^{-1}$; ^1H NMR (300 MHz, C_6D_6) δ 0.66 (s, 3H), 1.00 (s, 3H), 0.90−1.65 (m, 5H), 1.71−1−78 (dd, $J = 14, 8$ Hz, 1H), 1.84 (s, 3H), 1.94−2.04 (m, 1H), 2.24, 2.80 (AB, $J = 11$ Hz, 2H), 4.05−4.08 (dd, $J = 3, 7$ Hz, 1H), 5.25 (s, 1H) ppm; MS (DIP-CI−NH_3) $m/e = 483$ ($M^+ + 1 - CO$, 80), 528 ($M^+ + 18$, 25), 545 ($M^+ + 35$, 5). Internally chelated pentacarbonyl complex **10b**: brown spot on TLC ($R_f = 0.50$, SiO_2, hexanes/ethyl acetate 9/1); IR (film) $\nu_{max} = 2086, 2056, 2002, 1950\ cm^{-1}$; ^1H NMR (300 MHz, C_6D_6) δ 0.54 (s, 3H), 0.98 (s, 3H), 0.70−1.50 (m, 5H), 1.55−1.63 (dd, $J = 14, 8$ Hz, 1H), 1.60 (s, 3H), 1.88−1.96 (m, 1H), 2.00, 2.75 (AB, $J = 11$ Hz, 2H), 4.05−4.09 (dd, $J = 8, 4$ Hz, 1H), 4.94 (s, 1H) ppm.

General Procedures for Pauson−Khand Reaction: Adduct of 10a/10b with Norbornene (13). Reaction Conditions A. A solution of the dicobalt hexacarbonyl complex of *exo*-2-(ethynyloxy)-10-(methylthio)bornane (**10a**) (73 mg, 0.18 mmol) and norbornene (169 mg, 1.8 mmol) in hexane (10 mL) under CO atmosphere was stirred at room temperature. When TLC analysis showed complete consumption of the starting complex (20 h), the mixture was opened to the air for 5 h to induce the formation of insoluble cobalt salts and then filtered through a pad of Celite and the solvent removed in vacuo. Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/AcOEt, 2.5%) afforded 32 mg (65%) of **13** in the form of a 70:30 (40% de) mixture of diastereomers, as determined by ^1H NMR.

Reaction Conditions B. A solution of complex **10a** (161 mg, 0.31 mmol) in methylene chloride (17 mL) under nitrogen was treated with *N*-methylmorpholine *N*-oxide (221 mg, 1.8 mmol). When the reaction mixture was stirred at room temperature for 10 min, TLC analysis showed complete conversion of the starting red hexacarbonyl complex to the brown pentacarbonyl complex **10b**. The mixture was cooled at −20 °C, and a solution of norbornene (280 g, 3.0 mmol) in CH_2Cl_2 (1 mL) was added via syringe. The reaction was stirred at −20 °C overnight, the resulting purple mixture was filtered through a pad of Celite, and the filtrate was evaporated in vacuo. Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/AcOEt, 5%) afforded 84 mg (77%) of **13** as a 92:8 (84% de) mixture of diastereomers (^{13}C NMR). The major diastereomer could be isolated by column chromatography as a white crystalline solid. When the present procedure was followed but the cyclization performed at 0 °C, cyclopentenone **13** was otained in 66% yield and 76% de.

Reaction Conditions C. A solution of complex **10a** (82 mg, 0.16 mmol) in hexane (10 mL) was heated at 50 °C while being purged with a nitrogen stream. After 1 h, no further conversion to **10b** was visible by TLC (ca. 15:85 ratio of **10a**/**10b** as determined by NMR). The solution was then cooled at 0 °C, and a solution of norbornene (150 mg, 1.6 mmol) in hexane (1 mL) was added via syringe. The reaction mixture was stirred for 12 h at 0 °C and filtered through a pad of SiO_2 and the solvent removed in vacuo. This afforded 55 mg (99%) of **13** in the form of an 80:20 (60% de) mixture of diastereomers, as determined by ^{13}C NMR. When the reaction with norbornene was performed at 50 °C, the process took 10 min to completion and afforded cyclopentenone **13** in 69% yield and 20% de. Major diastereomer: mp 112−113 °C; $[\alpha]_D = -106.6$ (*c* 5, $CHCl_3$); IR (film) $\nu_{max} = 3060, 2950, 1710, 1610, 1330, 1300\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.05 (s, 3H), 0.90−2.20 (m, 15H), 2.06 (s, 3H), 2.35 (m, 1H), 2.50 (m, 1H), 2.50 (AB, $J = 11$ Hz, 1H), 2.96 (AB, $J = 11$ Hz, 1H), 4.12 (m, 1H), 6.17 (d, $J = 3$ Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.4 (CH_3), 20.2 (CH_3), 20.4 (CH_3), 27.0 (CH_2), 28.4 (CH_2), 28.8 (CH_2), 30.9 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 38.5 (CH), 38.7 (CH), 43.9 (CH), 45.4 (CH), 47.9 (C), 52.3 (CH), 53.2 (C), 83.2 (CH), 130.3 (CH), 157.4 (C), 204.0 (C═O) ppm; EM (CI-NH_3) $m/e = 347$ ($M^+ + 1$, 42), 364 ($M^+ + 18$, 100). Anal. Calcd for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.72; S, 9.25. Found: C, 72.50; H, 8.88; S, 9.14.

Pauson−Khand Adduct of 10a/10b with Norbornadiene (14). Reaction Conditions A. Following the general procedure described above, and starting from *exo*-2-(ethynyloxy)-10-(methylthio)bornane, **10a** (58 mg, 0.11 mmol) in hexane (7 mL), and norbornadiene (110 μL, 1.1 mmol), the reaction was conducted at room temperature for 4 h and yielded 37 mg (95% yield) of a 60:40 mixture of diastereomers **14** as determined by HPLC (Nucleosil C_{18}, 25 cm, H_2O/MeOH).

Reaction Conditions B. Complex **10b** was prepared from **10a** (2.31 g, 4.5 mmol) and *N*-methylmorpholine *N*-oxide (3.17 g, 27 mmol). For the cyclization, 4.5 mL (45 mmol) of norbornadiene was used, and the reaction temperature was −20 °C (overnight). Flash column chromatography (SiO_2/NEt_3, hexane/AcOEt, 5%) afforded 1.23 g (82%) of **14** as a 96:4 (92% de) mixture of diastereomers (by HPLC). The major diastereomer could be isolated by standard chromatography as a white solid. Major diastereomer: mp 58−60 °C; $[\alpha]_D = -95.2$ (*c* 7.3, $CHCl_3$); IR (film) $\nu_{max} = 3060, 2960, 1720, 1620, 1105\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.05 (s, 3H), 1.00−1.85 (m, 7H), 2.07 (s, 3H), 2.19 (m, 1H), 2.48 (AB, $J = 11$ Hz, 1H), 2.95 (AB, $J = 11$ Hz, 1H), 2.58 (m, 2H), 2.88 (s, 1H), 4.13 (m, 1H), 6.14−6.28 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5 (CH_3), 20.2 (CH_3), 20.5 (CH_3), 27.0 (CH_2), 30.9 (CH_2), 33.2 (CH_2), 38.3 (CH_2), 41.1 (CH_2), 42.5 (CH), 43.2 (CH),

(57) Longer deprotection times (K_2CO_3/MeOH) may result in the formation of methyl 3-(10-methylthioisobornyloxy)acrylate as a byproduct: ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.98 (s, 3H), 1.10−1.90 (m, 7H), 2.08 (s, 3H), 2.45−2−75 (AB, $J = 11$ Hz, 2H), 3.69 (s, 3H), 4.12 (m, 1H), 5.20, 7.60 (AB, $J = 12$ Hz, 2H) ppm.

43.4 (CH), 45.5 (CH), 47.9 (C), 50.3 (CH), 53.3 (C), 83.0 (CH), 130.8 (CH), 136.4 (CH), 138.2 (CH), 157.6 (C), 203.3 (C=O) ppm; HRMS (EI) calcd for $C_{21}H_{28}O_2S$ 344.1810, found 344.1813.

Pauson−Khand Adduct of 10a/10b with Bicyclo[3.2.0]-hept-6-ene (15). Reaction Conditions A. Reaction temperature: 50 °C (2h), 70% yield. Mixture of diastereomers (72: 28, 44% de) as determined by HPLC (Nucleosil C_{18}, 25 cm, H_2O/MeOH).

Reaction Conditions B. Reaction temperature: −20 °C (2 days), 91% yield. Mixture of diastereomers (93:7, 86% de) as determined by HPLC: colorless oil; $[\alpha]_D = -65.6$ (*c* 0.4, $CHCl_3$, 86% de mixture of diastereomers); IR (film) ν_{max}= 3060, 2950, 1715, 1615, 1125, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) mixture of diastereomers δ 0.89 (s, 3H), 1.06_{minor}, 1.09_{major} (s, 3H), 1.10−1.90 (m, 11H), 2.06_{major}, 2.09_{minor} (s, 3H), 2.30−2.62 (m, 5H), 2.98 (d, J = 10 Hz, 1H), 4.09−4.18 (m, 1H), 6.42_{major}, 6.44_{minor} (d, J = 3 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) major diastereomer δ 17.6 (CH_3), 20.3 (CH_3), 20.5 (CH_3), 24.9 (CH_2), 27.1 (CH_2), 31.0 (CH_2), 32.3 (CH_2), 32.9 (CH_2), 33.3 (CH_2), 38.3 (CH_2), 38.3 (CH), 38.7 (CH), 44.2 (CH), 45.6 (CH), 46.9 (CH), 48.1 (C), 53.5 (C), 83.6 (CH), 131.0 (CH), 156.1 (C) 204.5 (C=O) ppm; HRMS(EI) calcd for $C_{21}H_{30}O_2S$ 346.1966, found 346.1963.

Pauson-Kand Adduct of 11a/11b with Norbornadiene (16). Starting from dichloroolefin **8** (0.86 g, 2.45 mmol) and following the general procedure described for the preparation of **10a**/**10b**, complex **11a** contamined by minor amounts of **11b** (1.00 g, 72% yield) was obtained as a red oil. The Pauson−Khand reaction was then performed according to conditions B: reaction temperature −20 °C (overnight), 61% yield. Mixture of diastereomers (96:4, 92% de) as determined by HPLC (Nucleosil C_{18}, 25 cm, MeOH/H_2O): colorless oil; $[\alpha]_D = -83.8$ (*c* 1.1, $CHCl_3$, 92% de mixture of diastereomers); IR (film) ν_{max} = 3060, 2950, 1710, 1615, 1460, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) mixture of diastereomers δ 0.87 (s, 3H), 0.91 (s, 9H), 1.04 (s, 3H), 1.00−1.85 (m, 9H), 2.17 (d, J = 5 Hz, 1H), 2.29−2.68 (m, 5H), 2.83−3.02 (m, 2H), 4.08−4.20 (m, 1H), 6.14−6.33 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) mixture of diastereomers δ 20.7 (CH_3), 20.9 (CH_3), 27.5 (CH_2), 29.3 ($3CH_3$), 31.3 (CH_2), 32.9 (C), 33.7 (CH_2), 38.8 (CH_2), 41.5 (CH_2), 43.0 (CH), 43.7 (CH), 43.9 (CH), 46.1 (CH), 48.3 (C), 49.7 (CH2), 50.8 (CH), 53.8 (C), 83.5 (CH), 130.6_{minor}, 131.0_{major} (CH), 136.9 (CH), 138.7 (CH), 158.5 (C) ppm; HRMS (EI) calcd for $C_{25}H_{36}O_2S$ 400.2436, found 400.2438.

Pauson-Kand Adduct of 12a/12b with Norbornadiene (17). Starting from dichloroolefin **9** (0.35 g, 0.98 mmol) and following the general procedure described for the preparation of **10a**/**10b**, complex **12a** contamined with minor amounts of **12b** (0.40 g, 71% yield) was obtained as a red oil. The Pauson−Khand reaction was then performed according to conditions B: reaction temperature −20 °C (overnight), 65% yield. Mixture of diastereomers (93:7, 86% de) as determined by HPLC (Nucleosil C_{18}, 25 cm, MeOH/H_2O): $[\alpha]_D = -58.3$ (*c* 2.0, $CHCl_3$, 86% de mixture of diastereomers); IR (film) ν_{max} = 3050, 2950, 1715, 1615, 1130 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) mixture of diastereomers δ 0.97 (s, 3H), 1.08 (s, 3H), 1.00−1.90 (m, 9H), 2.11 (d, J = 5 Hz, 1H), 2.44 (m, 1H), 2.57 (s, 1H), 2.87 (s, 1H), 2.87−3.54 (AB, J = 12 Hz, 2H), 4.09 (m, 1H), 6.10−6.30 (m, 3H), 7.05−7.50 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) mixture of diastereomer δ 20.7 (CH_3), 21.0 (CH_3), 27.5 (CH_2), 31.4 (CH_2), 33.9 (CH_2), 38.8 (CH_2), 41.6 (CH_2), 43.0 (CH), 43.7 (CH), 48.8 (C), 46.0 (CH), 48.7 (C), 50.8 (CH), 53.6 (C), 82.9_{major}, 83.7_{minor} (CH), 126.2 (CH), 129.1 (CH), 130.6 (CH), 139.9 (CH), 136.9 (CH), 137.8 (C), 138.7 (CH), 158.0 (C) ppm; HRMS (EI) calcd for $C_{26}H_{30}O_2S$ 406.1966, found 406.1970.

General Procedure for Conjugate Additions: (−)-(1*R*,2*R*,4*R*,5*R*,6*R*, 7*S*)-4-[10-(Methylthioiso)borneoxy]-5-methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (19). Copper(I) iodide (0.55 g, 2.9 mmol) and 30 mL of ether were placed in a round-bottomed flask under nitrogen. The resulting slurry was cooled at −50 °C, and 1.6 M MeLi (3.4 mL, 5.4 mmol) was added via syringe. The mixture was stirred at −50 °C for 30 min and then allowed to gradually warm to −10 °C. A solution of **14** (diastereomeric mixture of 92% de) (0.5 g, 1.45 mmol) and chlorotrimethylsilane (0.4 mL, 2.9 mmol) in ether (5 mL) was added via cannula. A yellow solid immediately formed, and the reaction temperature was kept at −10 °C for 30 min and then at 0 °C for 3 h. The reaction crude was poured over a pH = 8 (NH_3/NH_4Cl) buffer solution, phases were separated, and the organic layer was washed with buffer solution until the aqueous phase did not turn blue. The aqueous phase was extracted with ether, and the combined organic extracts were dried (K_2CO_3) and concentrated in vacuo to yield the correponding silyl enol ether as a colorless oil. Without further purification, the crude silyl enol ether was dissolved in anhydrous THF (40 mL) under nitrogen, the solution was cooled at 0 °C, and a solution of tetrabutylamoniun fluoride (37 mg, 0.15 mmol) in anhydrous THF (1 mL) was added dropwise via syringe. When deprotection of the enol ether was complete (TLC), the reaction mixture was diluted with hexane, and saturated NH_4Cl solution was added until two clear phases formed. The organic layer was separated, washed with brine, dried (K_2CO_3), and concentrated in vacuo. Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/AcOEt, 1−2.5%) allowed a convenient separation of diastereomers at this stage and yielded 390 mg of **19** as a white solid (77%) and 15 mg of the minor isomer (3%). Major diastereomer: mp 55−56 °C; $[\alpha]_D = -104.0$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max}= 3060, 2980, 1750, 1150, 1080, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3H), 1.03 (s, 3H), 0.9 (m, 12H), 2.09 (s, 3H), 2,49, 3.12 (AB, J = 11 Hz, 2H), 2.73 (m, 1H), 3.18 (m, 1H), 3.80 (dd, J = 3, 7 Hz, 1H), 4.01 (dd, J = 2, 11 Hz, 1H), 6.13 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5 (CH_3), 19.1 (CH_3), 20.2 (CH_3), 20.8 (CH_3), 27.0 (CH_2), 30.6 (CH_2), 33.5 (CH_2), 39.1 (CH_2), 41.0 (CH), 43.4 (CH), 44.0 (CH), 44.6 (CH_2), 45.2 (CH), 45.9 (CH), 48.2 (CH), 85.3 (CH), 90.2 (CH), 136.2 (CH), 137.6 (CH), 213.9 (C=O) ppm; EM (DIP-CI-NH_3) m/e = 361 (M^+ + 1, 82), 378 (M^+ + 18, 100), 395 (M^+ + 35, 29). Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.94; S, 8.89. Found: C, 73.68; H, 9.28; S, 8.88. Minor diastereomer: ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.06 (s, 3H), 1.00−1.85 (m, 11H), 1.33 (d, J = 6 Hz, 3H), 2.01−2.20 (m, 1H), 2.11 (s, 3H), 2.38−2.89 (AB, J = 12 Hz, 2H), 2.76 (s, 1H), 3.15 (s, 1H), 3.58−3.68 (dd, J = 3, 7 Hz, 1H), 4.08−4.18 (dd, J = 2, 11 Hz, 1H), 6.08−6.20 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3 (CH_3), 19.2 (CH_3), 20.2 (CH_3), 20.6 (CH_3), 27.1 (CH_2), 31.1 (CH_2), 34.1 (CH_2), 40.1 (CH_2), 40.5 (CH), 43.3 (CH), 44.3 (CH), 44.6 (CH_2), 45.1 (CH), 45.8 (CH), 47.7 (C), 49.0 (CH), 53,5 (C), 85.3 (CH), 91.5 (CH), 136.9 (CH), 137.7 (CH), 215.2 (C=O) ppm.

(−)-(1*R*,2*R*,4*R*,5*R*,6*R*,7*S*)-4-[10-(Methylthio)isoborneoxy]-5-butyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (20) was prepared according to the general procedure described above for conjugate additions: Copper(I) cyanide (0.42 g, 4.7 mol) in ether (50 mL), *n*-BuLi 1.47 M in hexane (6.5 mL, 9.5 mmol), **14** (diasteromeric mixture of 92% de) (0.82 g, 2.4 mmol), and TMSCl (1.2 mL, 9.5 mmol) were used. Deprotection of the silyl enol ether was performed with tetrabutylamonium fluoride (63 mg, 0.24 mmol) in THF (1 mL). Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/ether, 1%) afforded 67 mg of a mixture of diastereomers and 0.76 g of the major diastereomer **20** as a colorless oil (81% overall yield). Major diastereomer: $[\alpha]_D = -107.1$ (*c* 1.3, $CHCl_3$); IR (film) ν_{max} = 3060, 2960, 1750, 1140, 1110, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.95 (t, J = 6 Hz, 3H), 1.03 (s, 3H), 1.10−1.90 (m), 2.08 (s, 3H), 2.14 (d, J = 10 Hz, 1H), 2.47−3.14 (AB, J = 12 Hz, 2H), 2.72 (s, 1H), 3.17 (s, 1H), 3.78−3.84 (dd, J = 3, 7 Hz, 1H), 4.01−4.08 (m, 1H), 6.08−6.20 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 17.5 (CH_3), 20.2 (CH_3), 20.8 (CH_3), 22.9 (CH_2), 29.4 (CH_2), 30.7 (CH_2), 33.5 (CH_2), 34.4 (CH_2), 39.0 (CH_2), 42.3 (CH), 43.5 (CH), 44.4 (CH_2), 45.3 (CH), 45.6 (CH), 47.4 (CH), 48.6 (C), 49.3 (CH), 53.3 (C), 85.4 (CH), 89.0 (CH), 136.8 (CH), 137.7 (CH), 214.3 (C=O) ppm; EM (DIP-CI-NH_3) m/e = 403 (M^+ + 1, 100), 420 (M^+ + 18, 25); HRMS (EI) calcd for $C_{25}H_{38}O_2S$ 402.2592, found 402.2587.

(−)-(1*R*,2*R*,4*R*,5*R*,6*R*,7*S*)-4-[10-(Methylthio)isoborneoxy]-5-phenyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (18) was prepared according to the general procedure described above for conjugate additions: CuBr−SMe_2 (0.25 g, 1.23 mol) in ether (6 mL), PhLi 1.6 M in ether (1.5 mL, 2.46 mmol), **14** (diasteromeric mixture of 92%) (138 mg, 0.41 mmol), and TMSCl

(153 μL, 1.2 mmol) in ether (2 mL) were used. Cuprate formation was run at 0 °C for 30 min. Substrate addition was performed at −78 °C, and then the reaction mixture was stirred at room temperature for 8 h. Addition of tetrabutylamonium fluoride (10 mg, 0.41 mmol) in THF (1 mL) at 0 °C resulted in complete deprotection of the silyl group. Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/ether, 1−5%) afforded 5 mg of the minor diastereomer and 92 mg of the major diastereomer **18** as a colorless oil (66% global yield). Major diastereomer: $[\alpha]_D = -57.6$ (*c* 1.0, $CHCl_3$); IR (film) $\nu_{max} = 3060, 2960, 1745, 1140, 690$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (s, 3H), 0.82 (s, 3H), 0.80−1.00 (m, 2H), 1.20−1.55 (m, 7H), 2.09 (s, 3H), 2.13−2.60 (m, 4H), 2.78 (s, 1H), 3.09 (d, $J = 11$ Hz, 1H), 3.24−3.33 (m, 2H), 4.60−4.67 (dd, $J = 2, 12$ Hz, 1H), 6.04−6.18 (m, 2H), 7.23−7.45 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.4 (CH_3), 20.0 (CH_3), 20.6 (CH_3), 26.8 (CH_2), 30.5 (CH_2), 33.6 (CH_2), 39.0 (CH_2), 43.8 (CH), 44.3 (CH_2), 44.9 (2 CH), 45.9 (CH), 47.4 (C), 49.0 (CH), 53.2 (C), 53.6 (CH), 86.0 (CH), 91.6 (CH), 126.8 (CH), 128.0 (2 CH), 128.5 (2 CH), 137.0 (CH), 137.7 (CH), 142.9 (C), 212.6 (C=O) ppm; EM (DIP-CI-NH_3) *m/e* = 423 ($M^+ + 1$, 100), 440 ($M^+ +$ 18, 6); HRMS (EI) calcd for $C_{27}H_{34}O_2S$ 422.2279, found 422.2282.

(−)-(1*R*,2*S*,5*S*,6*S*,7*S*)-5-Methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (22).[25a] Powder samarium metal (0.39 g, 2.6 mmol) and 1,2-diiodoetane (0.67 g, 2.4 mmol) were placed in an oven-dried Schlenk flask under argon atmosphere. Anhydrous THF (5 mL) was added via syringe, and the resulting slurry was stirred at room temperature for 1−2 h. This resulted in a deep blue solution of SmI_2. The reaction mixture was cooled at 0 °C, and a solution of **19** (290 mg, 0.8 mmol) in THF/MeOH 2/1 (2.5 mL) was added. The mixture was stirred at 0 °C for 5 min and then diluted with anhydrous THF first and finally with wet THF in order to deactivate the excess samarium diiodide.[58] The mixture was diluted with hexane and treated with saturated K_2CO_3. The aqueous phase was extracted with ether, and the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. Flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/AcOEt, 1.5%) afforded 153 mg (95% yield) of 10-(methylthio)isoborneol and 122 mg (93%) of (−)-(1*R*,2*S*,5*S*,6*S*,7*S*)-5-methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (**22**) as a colorless oil. $[\alpha]_D = -121.6$ (*c* 3.6, $CHCl_3$); IR (film) $\nu_{max} = 3070, 2970, 1740, 700$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (d, $J = 6$ Hz, 3H), 1.15−1.25 (m, 1H), 1.38−1.48 (m, 1H), 1.75−1.98 (m, 2H), 2.15−2.70 (ABX, $J_{ab} = 18$ Hz, $J_{ax} = 7$ Hz, $J_{bx} = 10$ Hz, 2H), 2.28−2.35 (m, 1H), 2.78 (s, 1H), 3.09 (s, 1H), 6.10−6.22 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 (CH_3), 33.9 (CH), 44.5 (CH_2), 45.2 (CH), 47.3 (CH), 51.2 (CH), 51.3 (CH_2), 55.2 (CH), 137.4 (CH), 138.4 (CH), 218.7 (C=O) ppm; EM (DIP-CI-NH_3) *m/e* = 114 ($C_6H_8O^+ +$ 18, 37), 163 ($M^+ + 1$, 1), 180 ($M^+ + 18$, 100), 197 ($M^+ + 35$, 18).

(−)-(1*R*,2*S*,5*S*,6*S*,7*S*)-5-Butyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (23).[33] Reductive cleavage of **20** (0.3 g, 0.76 mmol) with SmI_2 was performed following the same procedure as for the preparation of **22** and yielded 153 mg (99%) of 10-(methylthio)-isoborneol and 154 mg of **23** (88%) as a colorless oil: $[\alpha]_D = -122.0$ (*c* 1.3, $CHCl_3$); IR (film) $\nu_{max} = 3060, 2920, 1735, 1460, 1190, 690$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, $J = 6$ Hz, 3H), 1.10−1.80 (m, 9H), 1.94−2.01 (dd, $J = 5, 8$ Hz, 1H), 2.15−2.26 (m, 1H), 2.29 (d, $J = 9$ Hz), 2.54−2.67 (dd, $J = 18, 8$ Hz, 1H), 2.76 (s, 3H), 3.09 (s, 1H), 6.10−6.27 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.8 (CH_2), 30.0 (CH_2), 37.5 (CH_2), 39.3 (CH_2), 44.5 (CH_2), 45.2 (CH), 48.0 (CH), 49.6 (CH), 49.8 (CH_2), 54.9 (CH), 137.4 (CH), 138.4 (CH) ppm.

(+)-(*R*)-3-Methylcyclopentanone Semicarbazone 25.[34] To a solution of **23** (80 mg, 0.49 mmol) and maleic anhydride (250 mg, 2.5 mmol) in CH_2Cl_2 (3 mL) was added $MeAlCl_2$ 1 M in hexane (0.53 mL, 0.53 mmol) via syringe. Heating the reaction mixture at 55 °C for 1.5 h resulted in complete consumption of the starting material (TLC). The reaction mixture was then cooled at room temperature, quenched with saturated K_2CO_3 solution, filtered through Celite, and dried with $MgSO_4$. The CH_2Cl_2 solution of (−)-(*S*)-4-methyl-2-cyclopentenone (**24**) was diluted with MeOH (6 mL) and hydrogenated using Pd/C (10%) at atmospheric pressure (H_2, balloon). After 2 h, the complete disappearance of **24** could be observed by TLC. The catalyst was then removed by filtration through Celite, and the filtrate was treated with AcONa (0.3 g), semicarbazide hydrochloride (0.2 g), and water (2 mL). The resulting solution was heated at 80 °C for 1.5 h; organic solvents were then evaporated in vacuo, and the remaining aqueous phase was extracted with chloroform. The chloroform extract was dried (Na_2CO_3) and evaporated in vacuo. Flash column chromatography of the residue (SiO_2, $CHCl_3$/MeOH) yielded 55 mg (72%) of the corresponding semicarbazone **25** as a white solid: mp 170 °C (lit.[34] mp 173−174 °C); $[\alpha]_D = +38.5$ (*c* 1.0, $CHCl_3$) (lit.[35] $[\alpha]_D = +41.4$ (*c* 0.7, $CHCl_3$)); IR (KBr) $\nu_{max} = 3460, 2960, 1690, 1220, 1080$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (t, $J = 6$ Hz, 3H), 1.20−2.60 (m, 7H), 5.60 (s broad, 2H), 8.0 (NH, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5 (CH_3), 20.0 (CH_3), 27.2 (CH_2), 32.7 (CH_2), 32.8 (CH_2), 33.0 (CH_3), 33,4 (CH), 35.5 (CH_2), 41.3 (CH_2) ppm; EM (DIP-CI-NH_3) *m/e* = 156 ($M^+ + 1$, 50), 173 ($M^+ +$ 18, 100), 190 ($M^+ + 35$, 12).

(−)-(*S*)-4-Butyl-2-cyclopentenone (26).[59] In a round-bottomed flask under nitrogen were placed **23** (130 mg, 0.63 mmol), maleic anhydride (0.3 g, 3.1 mmol), and CH_2Cl_2 (4 mL). To this solution was added $MeAlCl_2$ (1 M in hexane, 0.7 mL, 0.7 mmol) via syringe. The reaction mixture was then heated at 55 °C for 2 h, cooled to room temperature, quenched with saturated K_2CO_3 solution, and filtered through Celite. The residue was purified by flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/ether) and afforded 85 mg (90%) of (−)-(*S*)-4-butyl-2-cyclopentenone as a colorless oil: $[\alpha]_D = -160.8$ (*c* 1.7, $CHCl_3$); IR (film) $\nu_{max} = 2960, 1710, 1585, 1180$ cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, $J = 7$ Hz, 3H), 1.15−1.70 (m, 6H), 1.95−2.60 (ABX, $J_{ab} = 19$ Hz, $J_{ax} = 2$ Hz, $J_{bx} = 6$ Hz, 2H), 2.85−3.00 (m, 1H), 6.14, 7.64 (AMX, $J_{am} = 5$ Hz, $J_{ax,mx} = 2$ Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9 (CH_3), 22.6 (CH_2), 29.7 (CH_2), 34.4 (CH_2), 41.0 (CH_2), 41.4 (CH_2), 133.5 (CH), 168.8 (CH), 210.2 (C=O) ppm.

(−)-2,3-Butanediol Acetal of the (*R*)-3-Butylcyclopentenone (27). A solution of **26** (78 mg, 0.56 mmol) in MeOH (8 mL) was hydrogenated over 10% Pd/C (13 mg) at atmospheric pressure (H_2, balloon). The hydrogenated mixture was filtered through Celite, and methanol was evaporated. The resulting residue was placed in a micro Dean−Stark apparatus along with (−)-2,3-butanediol (156 mg, 1.68 mmol), a catalytic amount of camphorsulfonic acid, and toluene. The mixture was heated at reflux for 6 h. The solvent was evaporated and the crude purified by flash column chromatography (2% v/v NEt_3 pretreated SiO_2, hexane/ether, 2%) to give 87 mg of acetal **27** (73% yield) as a colorless oil: IR (film) ν_{max}= 2930, 1450, 1375, 1310, 1110 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.00−1.55 (m, 14H), 1.65−2.08 (m, 5H), 3.47−3.62 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 16.8 (CH_3), 19.9 (CH_3), 22.7 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 35.5 (CH_2), 37.9 (CH), 38.0 (CH_2), 44.9 (CH_2), 78.0 (CH), 78.1 (CH), 117.0 (C) ppm; EM (DIP-CI-NH_3) *m/e* = 213 ($M^+ + 1$, 91).

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(58) Extended reduction times may result in overreduction of **22**. In this case, the corresponding alcohol can be reoxidized with PCC.

(59) Ackroyd, J.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 338−344.