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A Sterically-Encumbered, C_2-Symmetric Chiral Acetal for Enhanced Asymmetric Induction in the Pauson−Khand Reaction

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Abstract: High levels of diastereoselection were achieved in the PKR of 1,6- and 1,7-cyclopropylidenynes bearing a bulky propargylic C_2-symmetric acetal.

Asymmetric induction to generate optically active cyclopentenones is an ongoing challenge in the Pauson−Khand reaction (PKR).[1,2] Undeniably, realization of this goal augments the already high synthetic value of this method. Approaches envisaged in achieving varying degrees of asymmetry in the cobalt-mediated PKR include (a) utility of a chiral auxiliary bound to either reacting units, (b) generation of cobalt complexes possessing a disymmetric C_2Co_2 core,[3] (c) addition of a chiral promoter or coordinating ligand,[4] and (d) a combination of the first two strategies.[5]

Our study relies on the first strategy in which a chiral auxiliary is incorporated as a control element adjacent to the alkyne moiety. Used in early studies on stereoselective PKRs, chiral *trans*-2-phenylcyclohexanol[6,7] was successfully applied to the syntheses of (+)-hirsutene,[6] (+)-β-cuparenone,[8] and (+)-brefeldin A.[9] Enol and ynol ethers of Oppolzer's 3-(neopentyloxy)isoborneol also induced a highly diastereoselective PKR,[7] as shown in the syntheses of angular triquinane ring systems[10] and (+)-15-norpentalenene.[11] The technology later evolved to the use of sulfur-containing chiral auxiliaries, where the first generation of this type, *N*-(2-alkynoyl) derivatives of chiral oxazolidinones and sultams, e.g., Oppolzer's 10,2-camphorsultam, promoted exceptionally high levels of regio- and stereoselective intermolecular PKR.[12] A sulfinyl group, when bound to the alkene, induced complete stereoselectivity in the intramolecular variant,[13] and a phenylsulfonyl group in 3-oxygenated 1,6-enynes rendered endo stereochemical control.[14] Optically pure alkynyl *p*-tolyl sulfoxides resulted only in moderate yields and low selectivities in intermolecular PKRs.[15] Similarly, chiral acetylene thioethers provided low selectivity in both inter- and intramolecular cyclizations.[16] Finally, a new generation of chelating auxiliaries derived from camphor has emerged that combines the advantages of strategies (a) and (b) and benefits from the directed (or chelated)-PKR technology.[11,17,18]

Meanwhile, de Meijere and co-workers reported the construction of an enantiopure spiro(cyclopropane-1,4′-bicyclo[3.3.0]oct-1-en-3-one), **4**, derived from a diastereoselective PKR of a 1,6-cyclopropylidenyne bearing a propargylic C_2-symmetric chiral acetal (Scheme 1).[19,20] It was conceived that a larger alkyl group (R = $C(CH_3)_2$-OCH_3)[21] in a tartrate-derived chiral auxiliary, as in diol **5**, should improve the diastereoselectivity of the cycloaddition. Herein, we disclose our studies toward this end, including its scope, limitations, and implications.

The chiral diol **5** was prepared directly from (+)-dimethyl-L-tartrate, **1**.[21] Synthesis of the (cyclopropylidenepropyl)ethynyl dioxolanes parallels the route described by de Meijere (Scheme 2). Benzyl 4-cyclopropylidenebutanoate **7** was best prepared from the Wittig reaction of benzyl 4-oxobutanoate ester and cyclopropy-

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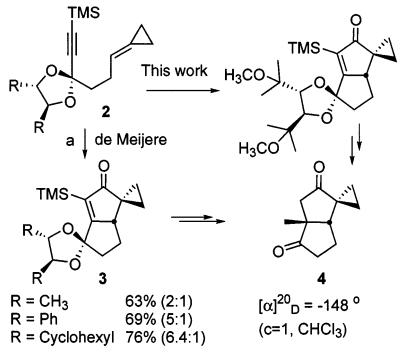
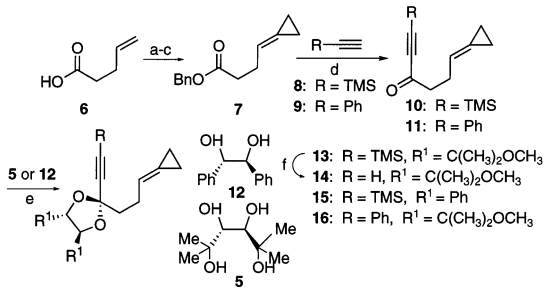
SCHEME 1[a]



[a] Key: (i) $Co_2(CO)_8$; (ii) CH_2Cl_2, rt, 6 equiv of NMO (Ar, 10 h) or 5 equiv of Me_3NO (O_2, 12−16 h).

SCHEME 2[a]

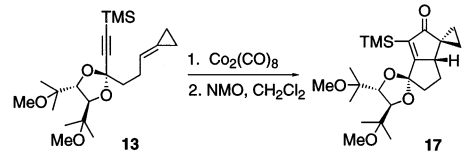


[a] Reagents and conditions: (a) benzyl alcohol, benzene, reflux, 99%; (b) (i) O_3, CH_2Cl_2, −78 °C, (ii) Me_2S, Et_3N, −78 °C to rt, 80% to quant; (c) cyclopropyltriphenylphosphonium bromide, NaH, cat. TDA-1, THF, reflux, 68%; (d) (i) **8** or **9**, *n*-BuLi, THF, −78 °C, (ii) **7** and then $BF_3{\cdot}Et_2O$, −78 °C to rt, **10**: 71%; **11**: 78%; (e) **5** or **12**, *i*-PrOTMS, catalytic TMSOTf, CH_2Cl_2, −30 °C to rt, **13**: 74%; **15**: 98%; **16**: 30%; (f) HF/pyridine, acetonitrile, **14**, 85%.

lidene triphenylphosphorane, in the presence of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) as a phase-transfer catalyst.[22] For optimal results in the Wittig reaction, we determined that a large excess of dry Wittig salt (6−10 equiv), generation of the phosphorane under refluxing conditions for an extended period of time (8−10 h), and use of a phase-transfer catalyst, TDA-1, were required. 6-Cyclopropylidene-1-hexyne-3-ones **10** and **11** were synthesized by reactions of ester **7** with the corresponding lithium alkynyltrifluoroborates of **8** and **9**, prepared in situ by addition of $BF_3{\cdot}Et_2O$ to the corresponding lithium acetylides at −78 °C in THF.[23] A modified Noyori acetal formation of **10** and **11** with diols **5** or **12** using *i*PrOTMS and catalytic amounts of TMSOTf afforded the appropriate acetals **13**, **15**, and **16**.[24] Compound **14** bearing a terminal alkyne moiety was easily obtained from desilylation of enyne **13**.

A series of *N*-methylmorpholine-*N*-oxide (NMO)-promoted PK reactions with the preformed dicobalthexacarbonyl complex of chiral (cyclopropylidenepropyl)ethynyldioxolane **13** was carried out to survey the optimal reaction conditions for diastereoselection (Table 1). Results show the reproducibility and high diastereoselectivity in the PK reactions of **13** indicating marked improvement over the previous report as a result of using a more sterically hindered chiral auxiliary from diol **5**. Despite its high degree of substitution, the dicobalthexacarbonyl complex of enyne **13** cyclized quite well providing 58−79% yields of the major diastereomer. Results indicated higher diastereomeric ratios of the products (1:15−20) when NMO was added as a solution in CH_2Cl_2 rather than as a solid (entry 2 vs 1). Dilution of the reaction mixture resulted in a slight erosion of selectivity (entry 2 vs 3). Incremental addition of NMO as a solution in CH_2Cl_2 at ambient temperature (entry 4), and at 0 °C with subsequent warming to ambient temperature (entry 5) gave lower selectivities and yields.

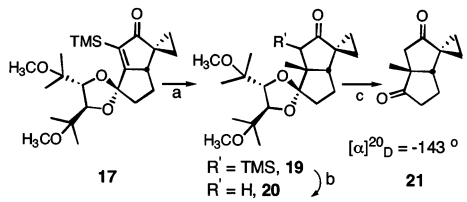
TABLE 1



entry	NMO-mediated cyclization conditions[a]	% yield (diastereomer ratio)[c]
1	5 equiv of NMO (solid), 0.03 M CH_2Cl_2[b]	79 (1:10)[d]
2	5 equiv of NMO, 0.03 M CH_2Cl_2	68 (1:15−20)[e]
3	5 equiv of NMO, 0.003 M CH_2Cl_2	65 (1:10−13)[e]
4	1 equiv of NMO (5×), 1.5 h interval, 0.03 M CH_2Cl_2	58 (1:11)[f]
5	1.5 equiv of NMO (5×), 1.5 h interval, 0.03 M CH_2Cl_2, 0 °C to rt	64 (1:9)

[a] All reactions were conducted under an Ar atmosphere at rt unless specified. [b] Reaction conditions as reported by de Meijere.[6] [c] Determined from 300 MHz ^1H NMR spectroscopy. [d] Average chromatographed yields of the major diastereomer from three trials. [e] four trials. [f] two trials.

SCHEME 3[6,a]



[a] Reagents and conditions: (a) Me_2CuLi, Et_2O, 0 °C, 92%; (b) 25 mol % pTSA, acetone, rt, 85%; (c) 60 mol % pTSA, acetone, 65 °C, 45%.

Several important observations were made in these studies. First, addition of the oxidant (NMO) as a solid resulted in a lower selectivity compared to addition as a solution (Table 1, entry 1 vs 2). Second, using our best reaction conditions (Table 1, entry 2), cyclization of enyne **15** occurred with lower diastereoselectivity (1:10) than cyclization of enyne **13**. In our hands, cyclization of **15** under de Meijere's conditions[19] gave the major diastereomer in 68% yield (1:5 dr), which is in agreement with their findings. Third, only 42% of the major diastereomer was isolated from a mixture of two diastereomers and decomplexed starting material (3:1:1) obtained after thermal reactions (0.02 M in toluene, 105 °C, N_2).

To ascertain the absolute configuration of the newly generated asymmetric center, the major diastereomer **17** was subjected to a series of transformations as previously described (Scheme 3).[19] De Meijere observed that direct hydrolysis of the acetal in **18** resulted in not only an

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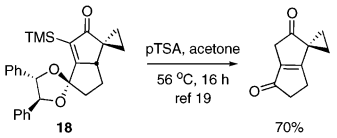
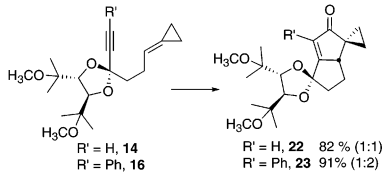
acetal cleavage but also double bond isomerization to give the bicyclo[3.3.0]octenedione (eq 1).[19] In our case, attempted hydrolysis of the acetal moiety[25] in enone **17** under the following reaction conditions only gave the unreacted enone **17**: (a) 5 mol % pTSA, acetone, ambient temperature to reflux; (b) 25 mol % pTSA, acetone, reflux; (c) 2 N HCl, THF, ambient temperature; and (d) acetone/H_2O/60% $HClO_4$ (10:1:1), ambient temperature. Thus, **17** was functionalized as previously reported.[19] Lithium dimethylcuprate addition and followed by protiodesilylation of α-keto silane **19** furnished ketone **20** in high yield. Subsequent acid-catalyzed hydrolysis of dioxolane **20** gave a good yield of dione **21** whose optical rotation $[\alpha]^{20}_D = -143$ is consistent with the reported value.[19] The C-5 position in the cycloadduct generated in this fashion was reported to have an *R* absolute configuration. As indicated earlier the origin of this diastereoselectivity is determined at the metallacycle-forming step in the proposed mechanism of the PK reaction.[19a]



18 70% (1)

We proceeded to investigate the effect of alkyl substitution on the alkene and alkyne moieties on the stereochemical outcome of the cyclization. As shown in Table 1 and eq 2, variation of the alkyne substituents (R′ = H, Ph, TMS) revealed the necessity of a bulky group, such as TMS on the alkyne component to induce asymmetry.[26] Enyne **14**, bearing a terminal acetylene, cyclized nonselectively, a result consistent with de Meijere's findings with the analogous desilylated **15**.[19] A marked improvement in diastereoselection was observed when the alkyl group was modified from R′ = H (**14**) to the largest R′ = TMS (**13**). These results indicate that the TMS group could serve as a "pro-H" taking advantage of its high diastereoselective influence in the PKR.[27]

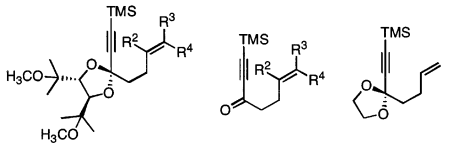


(2)

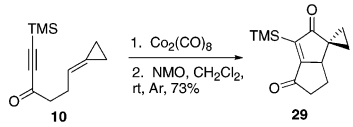
Key: 1) $Co_2(CO)_8$. 2) 5 equiv NMO (s), CH_2Cl_2 (0.03 M), rt, Ar

Changing the alkene substitution in these systems further confirmed the enhanced reactivity observed from methylenecyclopropane terminators in the PK reaction (Scheme 4).[28] It was noted by de Meijere's studies that enynes without this end group reacted poorly and only under more drastic conditions (hexanes, 110 °C) to provide the same selectivity. NMO-promoted or thermally mediated cyclizations (with or without an additive) of the dicobalthexacarbonyl complexes of enynes **24** and **25** gave only decomplexed starting materials. Their corresponding propargylic ketones **26** and **27** did not cyclize under these

SCHEME 4



conditions, although de Meijere obtained the cycloadduct of enyne **26** in 32% yield upon heating its cobalt complex in acetonitrile at 80 °C. These results suggest that the steric requirements imposed by the bulky auxiliary are not the only factor contributing to its lack of reactivity, as is also evident from the lack of reactivity of enyne **28**. In contrast, enyne **13** (vide supra) and keto enyne **10** (eq 3), both possessing the methylenecyclopropane moiety furnished the cyclopentenone in good yields under the NMO-promoted conditions. Meanwhile, the lack of reactivity of an analogous isopropylidene moiety (R^2 = H, $R^3 = R^4 = CH_3$) is well precedented in the literature.[29] Use of the activated methylenecyclopropane end group as in enyne **13** provides an access to the dimethyl-substituted bicyclopentenone ring upon reduction of the spirocyclopropyl moiety in enone **17** or **29**.[30]



10 **29** (3)

We also investigated the cyclizations of the homologous 7-cyclopropylidene-1-heptyne-3-ones bearing the propargylic acetal derived from diol **5**. The chiral acetals of 7-cyclopropylidene-1-heptyne-3-ones **36** and **37** were prepared in a straightforward manner from 5-hexen-1-ol (Scheme 5), and the corresponding dicobalthexacarbonyl complexes were subjected to various PKR conditions (Table 2). As is evident from the ^{1}H NMR spectra of the crude reaction mixtures using **36**, only one diastereomer could apparently be detected from all of the conditions used. Similar results were also observed from reaction of the analogous enyne **37**, which was derived from the less hindered chiral diol **12**. Under the conditions used in Table 2, we were not able to obtain the other diastereomeric product in either case for spectral comparison. Enone **39** and its diastereomer, as prepared by de Meijere,[19] although indistinguishable by ^{1}H NMR spectroscopy and TLC, showed different resonances in the ^{13}C NMR spectrum. They ultimately determined the structure of enone **39** by crystallographic separation and X-ray crystallography.[19] Enones **38** and **39** obtained using our reaction conditions did not show any isomeric impurities in both the ^{1}H and ^{13}C NMR spectra.

(25) Greene, T. W.; Wutts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.

(26) Reported yields in eq 2 correspond to the mixture of diastereomers, and dr was determined by 300 MHz ^{1}H NMR spectroscopy.

(27) Krafft, M. E.; Wright, C. *Tetrahedron Lett.* **1992**, *33*, 151.

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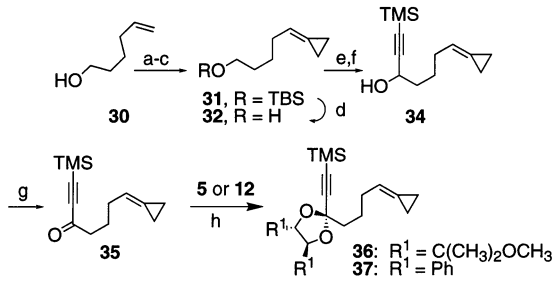
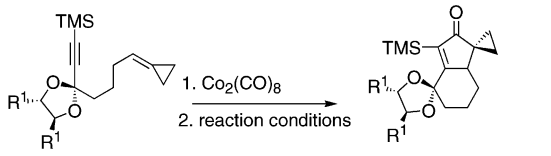
(30) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1984**, 959.

SCHEME 5[a]



[a] Reagents and conditions: (a) TBSCl, Et_3N, catalytic DMAP, CH_2Cl_2, 97%; (b) (i) O_3, CH_2Cl_2, (ii) Me_2S, Et_3N, 77%; (c) NaH, cyclopropyltriphenylphosphonium bromide, catalytic TDA-1, THF, reflux, 35%; (d) TBAF, THF, 80%; (e) PCC, CH_2Cl_2, 90%; (f) TMSCCH, *n*-BuLi, THF, −78 °C to rt, 55%; (g) PCC, CH_2Cl_2, 83%; (h) **5** or **12**, *i*-PrOTMS, cat. TMSOTf, CH_2Cl_2, −30 °C to rt, **36**, 65%; **37**, 89%.

TABLE 2



36, $R^1 = C(CH_3)_2OCH_3$
37, R^1 = Ph

38, $R^1 = C(CH_3)_2OCH_3$
39, R^1 = Ph

entry	cyclization conditions[a]	% yield[a] **38**	**39**
1	5 equiv of NMO (solid), 0.03 M CH_2Cl_2, rt, 18 h	41	ND
2	5 equiv of NMO, 0.03 M CH_2Cl_2, rt, 18 h	94	85
3	5 equiv of Me_3NO, 0.03 M CH_2Cl_2, −78 °C, 18 h	88	91
4	0.02 M toluene, 90−105 °C, N_2 1 h	63	89
5	9 equiv of $CyNH_2$, 0.01 M DCE reflux, N_2, 30 min	ND	73

[a] Average of two or three trials. ND = not determined.

Comparison of the cyclizations of 6-cyclopropylidene-1-trimethylsilyl-3-one acetal and the 7-cyclopropylidene analogue shows better diastereoselectivity in the latter system, as was noted by de Meijere (Scheme 1).[19b] In our case, when we subjected enynes **13** and **36** to de Meijere's reaction conditions (cf. Table 1, entries 1 and 2, and Table 2, entries 1 and 2) we also observed higher ratios of diastereomeric enones in both ring sizes using the more hindered acetal. Other reaction conditions used for the cyclization of **36** also gave high yields of one diastereomer.

In summary, as first reported by de Meijere, diastereoselective cyclizations of 1,6- and 1,7-cyclopropylidenynones bearing chiral C_2-symmetric acetals of propargylic ketones could be achieved in the PKR. We, on the other hand, have further shown that more sterically demanding substituents on the tartrate-derived auxiliary enhanced the stereoselection without loss of efficiency. In addition to the bulky substituent on the alkyne moiety, it was also demonstrated that the methylenecyclopropyl group in the precursor enyne is essential to reactivity of this system in the PKR. We have also provided modified reaction conditions to the ones originally reported that achieved optimal diastereoselection in the cyclizations.

Experimental Section

Acetal 13. To a cooled solution (−20 °C) of keto enyne **10** (28 mg, 0.14 mmol) and diol **5** (60 mg, 0.29 mmol) in CH_2Cl_2 (2.2 mL) were added successively ^{i}PrOTMS (0.15 mL, 0.84 mmol) and TMSOTf (4 drops). After being stirred for 14 h, with the bath warming to ambient temperature, the mixture was quenched with pyridine and poured into a solution of saturated $NaHCO_3$. It was then extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was washed with brine, dried ($MgSO_4$), and plugged through a short pad of coarse silica gel. Concentration in vacuo and purification by flash chromatography (SiO_2, 3% and then 2% EtOAc in hexanes) provided 40 mg of acetal **13** (74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.82 (tdt, J = 6.4, 4.1, 2.0 Hz, 1H), 4.14 (d, J = 5.2 Hz, 1H), 4.00 (d, J = 5.0 Hz, 1H), 3.22 (s, 3H), 3.21 (s, 3H), 2.43 (apparent dtm, J = 6.2, 6.2 Hz, 2H), 2.04 (m, 2H), 1.29 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H), 1.02 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 120.87, 117.61, 105.22, 104.87, 88.16, 84.27, 83.90, 75.75, 75.38, 49.00, 48.78, 41.11, 26.81, 22.14, 21.75, 20.46, 19.92, 1.65, 1.58, −0.58. MS [CI, *m*/*z* (rel intensity)]: 363.3 (100), 395.6 (M^+ + 1, 24). Anal. Calcd for $C_{22}H_{38}O_4Si$: C, 66.96; H, 9.71. Found: C, 67.04; H, 9.67. $[\alpha]^{20}_D$ −4.5 (*c* = 1, $CHCl_3$).

Representative Experimental Procedures. In all of the procedures described below, the dicobalthexacarbonyl complexed enynes were prepared just prior to the reactions. A typical procedure involved reaction of the enyne with the commercially available $Co_2(CO)_8$ in petroleum ether (0.2 M) at ambient temperature for 30 min or upon completion as determined by TLC. The complex was then filtered through a short plug of Celite (petroleum ether as solvent) and the solvent was removed in vacuo at ambient temperature.

General Procedures Used in Table 1. In entry 1, to a solution of the dicobalthexacarbonyl complex of enyne **13** (20 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was added NMO·H_2O (21 mg, 0.16 mmol) and the solution stirred at ambient temperature for 18 h. It was then diluted with EtOAc (10 mL) and plugged through a short pad of coarse silica gel. Concentration in vacuo and purification by flash chromatography (SiO_2, 3% EtOAc in hexanes) afforded 10 mg of enone **17** (83%). In entries 2 and 3, 5 equiv of NMO·H_2O in CH_2Cl_2 (0.50 M) was added in one portion to the reaction mixture (substrate concentration of 0.03 and 0.003 M, respectively). In entry 4, 1 equiv of a NMO−CH_2Cl_2 solution (0.50 M) was added five times to the reaction mixture (0.03 M substrate concentration) at 1.5 h intervals at ambient temperature. In entry 5, 1 equiv of a NMO−CH_2Cl_2 solution (0.50 M) was added five times to the reaction mixture (0.03 M substrate concentration) at 1.5 h intervals at 0 °C and the mixture warmed to ambient temperature. These reactions were typically worked up after 15−20 h.

Enone 17 was prepared according to the procedures described above and obtained as the major diastereomer. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.14 (d, J = 5.0 Hz, 1H, CHO), 4.09 (d, J = 5.0 Hz, 1H, CHO), 3.22 (s, 3H, OCH_3), 3.17 (s, 3H, OCH_3), 3.13 (t, J = 9.6 Hz, 1H, C*H*CH_2), 2.18 (ddd, J = 14.9, 9.6, 5.3 Hz, 1H, O_2-CC*H*H), 2.05 (br dddd, J = 14.0, 11.2, 5.3, 0.9 Hz, 1H, O_2CC*H*H), 1.88 (dtd, J = 12.4, 9.6, 5.3 Hz, 1H, C*H*HCH), 1.31−1.25 (m, 2H, 1 Cpr H, CH*H*CH), 1.23 (s, 3H, $C(CH_3)O$), 1.17 (s, 6H, 2 $C(CH_3)O$), 1.14 (s, 3H, $C(CH_3)O$), 0.88−0.99 (m, 3H, 3 Cpr-H), 0.24 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.00, 190.21, 133.93, 114.27, 85.39, 82.12, 75.66, 75.46, 49.13, 49.04, 47.44, 38.38, 34.40, 23.36, 22.19, 21.71, 20.76, 20.09, 15.18, 14.15, −0.12. MS [CI, *m*/*z* (rel intensity)]: 171.1 (44), 423.3 (100, M^+ + 1). Anal. Calcd for $C_{23}H_{38}O_5Si$·0.5 H_2O: C, 64.00; H, 8.87. Found: C, 64.07; H, 8.87. $[\alpha]^{20}_D$ −115 (*c* = 1, $CHCl_3$).

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Supporting Information Available: ^{1}H NMR spectra of compounds **16**, **23**, **27,** and **38** and experimental data for all other compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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