Diastereoselective Ester Enolate Alkylations. Asymmetric Syntheses of 3-Alkyl-3-carbomethoxy-2-*exo*-methylenecyclohex-5-en-1-ones

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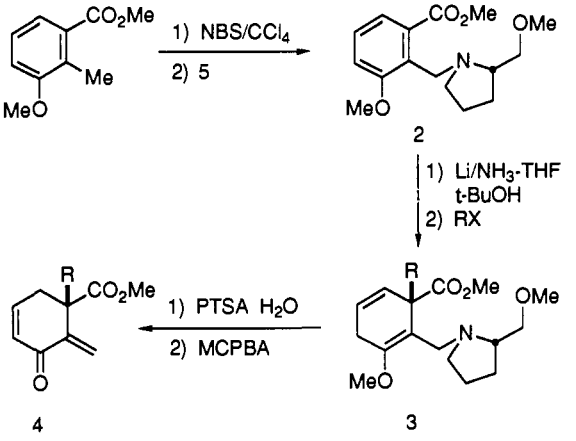
Abstract: Enolate **12**, designed to take advantage of potential chelation sites on the chiral auxiliary, (*S*)-2-(methoxymethyl)pyrrolidine, gives excellent diastereoselectivities for alkyl-, propargyl-, and cyanomethylations; negligible diastereoselectivities were observed for allyl- and benzylations. The resulting 3-substituted 3-carbomethoxy-1,4-cyclohexadienes **3a–g** were converted to 3-substituted 3-carbomethoxy-2-*exo*-methylenecyclohex-5-en-1-ones **4a–g**. Experiments designed to detect the possible involvement of single-electron transfer during alkylation of enolate **12** indicate that alkylations most probably occur via the S_N2 pathway.

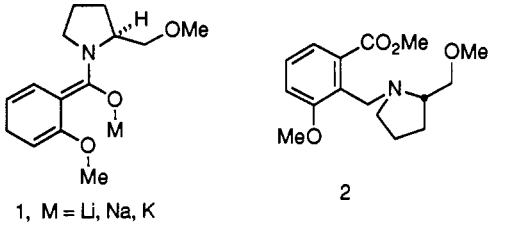
2-Methylenecycloalkanones are important intermediates in synthesis design primarily because of their ability to undergo inter- and intramolecular Michael additions and Diels–Alder reactions.[1] Several methods are available for the preparation of 2-methylenecycloalkanones. Most involve enolate condensation with formaldehyde or related synthetic equivalents.[1,2] Recently, Tamura, Yamamoto, and co-workers have disclosed an asymmetric synthesis of 3-substituted 2-*exo*-methylenecyclohexanones by a conjugate addition–chiral auxiliary elimination strategy.[3] Herein, we report enantioselective syntheses of 3-substituted 3-carbomethoxy-2-*exo*-methylenecyclohex-5-en-1-ones **4** by way of a new concept in stereodirected ester enolate alkylation: remote chelation control by the chiral auxiliary in the hypothetical enolate **12**. It is expected that cross-conjugated chiral dienones **4** will offer unique opportunities in synthesis design.[4]

Results and Discussion

Enolate **1** generated by Birch reduction of the corresponding 2-methoxybenzamide has been shown to have *Z*-configuration.[5a] The preference for *Z*-configuration presumably is a result of chelation of the alkali metal cation with the neighboring methoxy substituent. While this arrangement provides outstanding diastereoselectivities for enolate alkylations, little additional synthetic utility can be extracted from the chiral auxiliary,[5b] i.e., (*S*)-2-(methoxymethyl)pyrrolidine. Indeed, a separate amide hydrolysis step is generally required for removal of the chiral auxiliary.

Scheme I





Enolate alkylation studies with benzoic ester **2** were designed with the following considerations in mind:

1. The chiral auxiliary, (*S*)-2-(methoxymethyl)pyrrolidine, was positioned not only to provide stereocontrol in alkylations of the derived ester enolate but also to serve as a leaving group for generation of the 2-*exo*-methylene group in dienone **4**.

2. Stereoselectivity during alkylation was expected to be possible because of the opportunity for chelation of the alkali metal cation with the nitrogen and ether oxygen atoms of the chiral auxiliary.

3. Internal coordination of the alkali metal cation with the chiral auxiliary was expected to decrease the importance of aggregation effects and, therefore, simplify the interpretation of alkylation diastereoselectivities.

Methyl (*S*)-3-methoxy-2-[[2′-(methoxymethyl)pyrrolidinyl]-methyl]benzoate (**2**) was prepared from methyl 3-methoxy-2-methylbenzoate[6] by bromination with *N*-bromosuccinimide followed by treatment of the intermediate 2-(bromomethyl)benzoate

(1) For examples, see: (a) Tanaka, A.; Uda, H.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1967**, 188. (b) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114. (c) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745. (d) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146. (e) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 919. (f) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.* **1988**, *53*, 5590. (g) Tamura, R.; Tomai, S.; Katayama, H.; Suzuki, H. *Tetrahedron Lett.* **1989**, *30*, 3685.

(2) (a) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180. (b) Cassady, J. M.; Byrn, S. R.; Stamos, I. K.; Evans, S. M.; McKenzie, A. *J. Med. Chem.* **1978**, *21*, 815. (c) Shono, T.; Nishiguchi, I.; Komamura, T.; Sasaki, M. *J. Am. Chem. Soc.* **1979**, *101*, 984. (d) Block, E.; Aslam, M.; Iyer, R.; Huchinson, J. *J. Org. Chem.* **1984**, *49*, 3664. (e) Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3904. (f) Fleming, I.; Goldhill, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1493. (g) Ryu, I.; Matsumoto, K.; Ando, M.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1980**, *21*, 4283. (h) Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 598. (i) Tsuji, J.; Nisar, M.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 2483.

(3) (a) Tamura, R.; Watabe, K.; Katayama, H.; Suzuki, H.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 408.

(4) For the preparation of 6-*exo*-methylenecyclohex-2-en-1-one, see: Morris, I. G.; Pinder, A. R. *J. Chem. Soc.* **1963**, 1841. This substance was prepared by Birch reduction of 2-methoxy-*N*,*N*-dimethylbenzylamine, acid-catalyzed hydrolysis of the resulting 1,4-cyclohexadiene to 6-[(dimethylamino)methyl]cyclohex-2-en-1-one, and base-induced elimination of the derived methiodide (unspecified yield). To our knowledge, this represents the only reported synthesis of a cross-conjugated dienone of type **4**.

(5) (a) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207. (b) For exceptions to this statement, see ref 5a.

(6) Cresp, T. M.; Giles, R. G. F.; Sargent, M. V.; Brown, C.; Smith, D. O'N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2435. Prepared for this study by the method of Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

0002-7863/92/1514-3937$03.00/0

Table I. Stereoselectivities of Alkylation of Enolate **12**

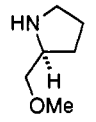
entry	product **3**	enolate treatment[a]	diastereomer distribution[b]	% yield (isolated)[c,d]
1	**a**, R = Me	none	13:1	89
2	**a**	warm to 0 °C; recool to −78 °C	20:1	83
3	**b**, R = Et	none	10:1	79
4	**b**	warm to 0 °C; recool to −78 °C	15:1	84
5	**c**, R = $CH_2CH_2CH_3$	none	10:1	78
6	**c**	warm to 0 °C; recool to −78 °C	15:1	75
7	**d**, R = CH_2Ph	none	<2:1	73
8	**d**	warm to 0 °C; recool to −78 °C	<2:1	–
9	**e**, R = $CH_2CH{=}CH_2$	none	1:1	79
10	**e**	warm to 0 °C; recool to −78 °C	<2:1	74
11	**f**, R = $CH_2C{\equiv}CH$	none	10:1	54
12	**f**	warm to 0 °C; recool to −78 °C	20:1	50
13	**g**, R = CH_2CN	none	>20:1	63
14	**g**	warm to 0 °C; recool to −78 °C	>20:1	54

[a] Enolate **12** was generated in each case by Birch reduction of **2** in NH_3–THF at −78 °C with 1 equiv of *t*-BuOH and 2.2 equiv of Li; 1,3-pentadiene was added to consume excess Li before addition of the alkyl halide. [b] Diastereomer distribution determined by ^1H NMR analyses of reaction mixtures. After chromatography on silica gel, **3a–g** were obtained in each case with diastereomer distributions ≥20:1. [c] Yields have not been corrected for unreacted starting material. [d] Diastereoselectivities were found to be independent of the leaving group on the alkylation reagent for MeI, MeBr, and MeOTs; BnBr, BnCl, and BnOTs; $CH_2{=}CHCH_2Br$ and $CH_2{=}CHCH_2OTs$; but more complex product mixtures were obtained with the sulfonate esters.

with (*S*)-2-(methoxymethyl)pyrrolidine (**5**)[7] (Scheme I). Birch reduction of **2** at −78 °C with lithium in NH_3–THF in the presence of *tert*-butyl alcohol (1 equiv) and alkylation of the resulting methyl ester enolate with alkyl halides gave the 3-alkyl-3-carbomethoxy-1,4-cyclohexadienes **3** in good to excellent yields (Table I).

Alkylation diastereoselectivities were excellent for alkyl-, propargyl-, and cyanomethylations, but were negligible for allyl- and benzylations. In general, stereoselectivities improved somewhat by evaporation of ammonia prior to addition of the alkyl halide to the enolate at −78 °C; addition of the alkylation reagent at 0 °C resulted in greatly reduced stereoselectivities (see Experimental Section).

A two-step protocol for removal of the chiral auxiliary was developed. Acid-catalyzed enol ether hydrolysis and olefin migration followed by treatment of the resulting β-amino enone with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 gave the 2-*exo*-methylenecyclohex-5-en-1-ones **4a–g**. Flash chromatography on silica gel provided good yields of dienones **4** except for the 3-allyl derivative **4e**; in this case, a 1:1 mixture of **4e** and methyl 2-(3′-butenyl)-3-hydroxybenzoate (**6**) was obtained. Heating this mixture in $CHCl_3$ solution to reflux resulted in quantitative Cope rearrangement of **4e** to **6**. Enantiomeric excesses of 88, 97, and 91% were determined for **4a**, **4b**, and **4g** by utilization of a chiral HPLC technique (see Experimental Section).



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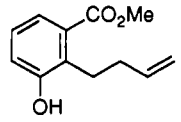

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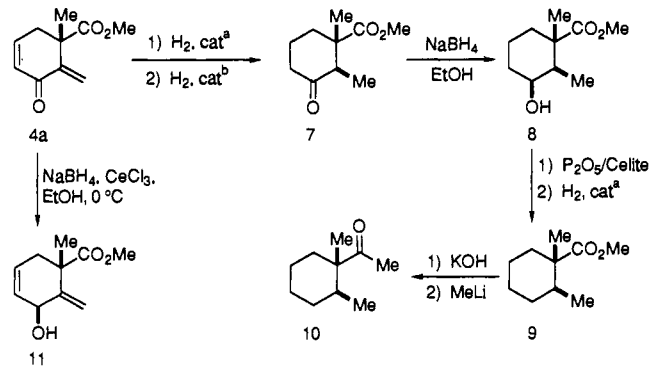
The absolute configuration of **4a** was determined by the chemical interconversions shown in Scheme II. It is expected that many of the reactions shown in Scheme II will have synthetic utility for C(3) alkyl analogues of **4a**. For this reason, the chemistry associated with these interconversions is discussed in some detail.

Ester-directed hydrogenation[8a] of **4a** with the homogeneous catalyst/solvent system $[Ir(cod)py(PCy_3)]PF_6/CH_2Cl_2$[8b] occurred regioselectively at the 2-*exo*-methylene group.[9] Subsequent

Scheme II[a]



[a] (a) Catalyst system: $[Ir(cod)py(PCy_3)]PF_6$ in CH_2Cl_2 at 1 atm. (b) Catalyst system: Rh on alumina in EtOAc at 1 atm.

hydrogenation of the C(5)–C(6) double bond with Rh on alumina gave a 14:1 mixture of diastereomers, from which **7** was obtained in 84% isolated yield by flash chromatography on silica gel. Epimerization of **7** with Na_2CO_3 in MeOH gave a 1:1 mixture of the diastereomers, indicating that little if any epimerization at C(2) occurs during hydrogenations of **4a**.

Sodium borohydride reduction of **7** gave alcohol **8**, possessing three contiguous stereogenic centers, in 97% yield. It is worth noting that inverted configuration at C(1) and C(2) of **8** would be anticipated from protiolactonization of the C(1)–C(2) olefin (vide infra) derived from **8**. Excellent stereoselectivity also was obtained for reduction of **4a** with $NaBH_4/CeCl_3$ in ethanol,[10] which gave bis-allylic alcohol **11** and its diastereomer (14:1) in 89% isolated yield.[11]

Dehydration of **8** with phosphorus pentoxide and Celite in benzene[12] provided a single olefin, 6-carbomethoxy-1,6-dimethylcyclohex-1-ene; ester-directed hydrogenation with the

(7) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173.
(8) (a) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905. (b) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.
(9) The regioselectivity for ester-directed hydrogenation is dependent on C(3) substitution. Hydrogenation of the benzyl analogue **4d** with 4 mol % $[Ir(cod)py(PCy_3)]PF_6$ occurred substantially faster than with **4a** to give the fully saturated analogue of **7**. Presumably the larger benzyl substituent enables the carbomethoxy ligand to more easily reside in the pseudoaxial conformation required for hydrogenation of both olefinic bonds.
(10) Gemal, A. L.; Luche, J.-L. *J. Org. Chem.* **1979**, *44*, 4187.
(11) Attempted crystallization of the *p*-bromobenzoate derivative of **11** (see Experimental Section for details) afforded only a few crystals. X-ray structural characterization established the relative configuration as indicated for **11**; however, it was found that the crystal selected for X-ray studies consisted of racemic material. Repeated attempts at crystallization of the mother liquor (now richer in the enantiomer corresponding to **11**) failed to produce crystalline material. Following this and other failures to deduce the absolute configuration of **4a** by X-ray crystallographic techniques, we chose to relate **4a** to a literature compound by chemical interconversion. For a discussion of the tendency of racemic crystals to be more stable than their chiral counterparts, see: Brock, C. P.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811.
(12) (a) Phalnikar, N. L.; Nargund, K. S. *Indian J. Chem.* **1963**, *14*, 736. (b) Schultz, A. G.; Sundararaman, P. *J. Org. Chem.* **1984**, *49*, 2455.

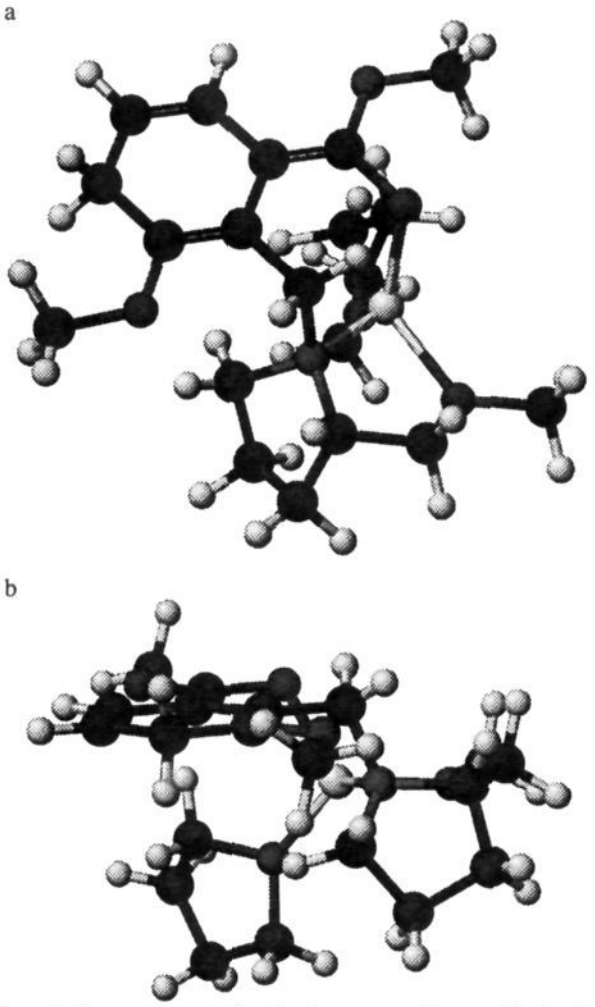
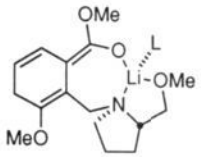


Figure 1. Computer-generated molecular structure of enolate **12**, wherein L = THF: (a) view of the relatively unobstructed β-face of the enolate; (b) view near the plane of the enolate showing the proximity of the C(5′) methylene unit of the chiral auxiliary and the ligand THF to the α-face.

iridium catalyst system gave **9** in 71% overall yield from **8**. Ester **9** was then converted to the previously described ketone **10**.[13] The optical rotation obtained for this material enabled an absolute configurational assignment to be made for **4a** and, by association, to other members of the series **4b–g**.[14]

The diastereoselectivities observed for lithium in ammonia reduction–alkylation of **2** are consistent with an intermediate enolate of structure **12**. Chelation of the lithium ion with the neighboring nitrogen and oxygen atoms of the chiral auxiliary imparts a high degree of rigidity to the enolate. A fourth ligand, L, coordinated to the lithium ion might be a solvent molecule or a second enolate (dimeric aggregate).[15] In either case, the α-face of the enolate would be relatively shielded from the alkylation reagent as a result of the proximity of the C(5′) methylene group of the chiral auxiliary and ligand L. These observations are clearly depicted in the computer-generated representation of enolate **12** (L = THF) shown in Figure 1.

The proposed seven-membered chelate unit in **12** is supported by X-ray crystallographic data reported for the chelated lithium



12

enolate of 2-[(dimethylamino)methyl]acetophenone.[16] X-ray diffraction studies also have shown that ether substituents can form five-membered chelate rings with lithium enolates of ketones.[17]

The absence of stereoselectivity for alkylations of **12** with benzylic and allylic halides is difficult to explain. We considered a change in mechanism from S_N2 for saturated alkyl halides to an electron-transfer process for benzylic and allylic halides, but have not found support for this explanation from the following observations:

1. Electron transfer from **12** to propargyl bromide and bromoacetonitrile also might be expected, but these alkylation reagents gave diastereoselectivities comparable to those of saturated alkyl halides.

2. Single-electron transfer has been proposed for a variety of reactions between organolithium compounds and alkyl halides.[18] For example, trityl chloride is reduced by hindered dialkyl amide bases in THF to give predominantly triphenylmethane.[18c] Treatment of enolate **12** at −78 °C with 1 equiv of trityl chloride for 30 min prior to addition of methyl iodide gave only **3a** with the usual 13:1 diastereomer distribution and recovered trityl chloride. Warming the solution of enolate and trityl chloride to ambient temperature (without addition of methyl iodide) did produce triphenylmethane and the aromatic substrate **2** after several hours; however, these reaction conditions appear to have little if any relevance to the enolate alkylation process.

3. Relative reaction rate data for alkylation of enolate **12** are compatible with an S_N2 mechanism; e.g., methyl iodide 1.0, propyl iodide <0.1, allyl bromide 1.5, benzyl bromide 3.4, and propargyl bromide 1.8.[19]

Conclusion

We have shown that it is possible to obtain excellent diastereoselectivities for alkylations of an enolate of a methyl ester that contains a remote chiral auxiliary. Stereocontrol appears to be a result of coordination of the alkali metal cation of the enolate with the nitrogen and oxygen atoms of the chiral auxiliary. It is expected that this design for asymmetric syntheses of chiral carboxylic acid derivatives will have synthetic utility. Applications involving the chemistry of 3-alkyl-3-carbomethoxy-2-*exo*-methylenecyclohex-5-en-1-ones will be reported in due course.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded at 200 MHz with chloroform as an internal standard. Solutions were concentrated by rotary evaporation. All reactions were stirred magnetically under nitrogen atmosphere. Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI. HPLC analyses were carried out using a chiral column (Diacel, Chiracel OJ) and hexane–*i*-PrOH (4:1) as solvent.

Methyl (*S*)-3-Methoxy-2-[[2′-(methoxymethyl)pyrrolidinyl]methyl]-benzoate (2). A solution of methyl 3-methoxy-2-methylbenzoate (1.00 g, 5.55 mmol), *N*-bromosuccinimide (1.18 g, 6.63 mmol), and benzoyl peroxide (6.0 mg, 0.25 mmol) in carbon tetrachloride (75 mL) was heated at reflux and carefully monitored by thin-layer chromatography

(13) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

(14) The major diastereomers **3a–c** each have greater retention times on silica gel than the corresponding minor diastereomers. As described in the Experimental Section, **3f** was related to **3c** and **3e** by hydrogenation studies. There is no reason to suspect opposite stereoselectivity for formation of **3g**.

(15) The dimeric aggregate is envisioned to contain a four-membered ring involving an additional coordination site on the enolate oxygen atom; see refs 16 and 17 for an example of dimeric lithium enolate complexes of this type.

(16) (a) Jastrzebski, J. T. B. H.; van Koten, G.; Christophersen, M. J. N.; Stam, C. H. *J. Organomet. Chem.* **1985**, *292*, 319. (b) For X-ray characterization of seven-membered chelate rings of a lithium enolate of a γ-siloxy ketone, see: Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

(17) Hintze, M. J. Ph.D. Thesis, Brown University, 1990.

(18) (a) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987**, *52*, 1291. (b) Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414. (c) Newcomb, M.; Varick, T. R.; Goh, S.-H. *J. Am. Chem. Soc.* **1990**, *112*, 5186.

(19) For reference data, see: Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; p 13.

(silica gel, hexane–ethyl acetate, 9:1). After 90 min, the reaction mixture was cooled to room temperature, filtered through glass wool into an addition funnel, and added dropwise to a stirred solution of (*S*)-2-(methoxymethyl)pyrrolidine (700 mg, 6.09 mmol), potassium carbonate (1.00 g, 7.25 mmol), and water (10 mL) in methylene chloride (75 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 15 h. The mixture was transferred to a separatory funnel and washed with water (2 × 50 mL), sodium thiosulfate (5%, 2 × 50 mL), and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give a yellow oil. Flash chromatography (alumina, hexane–ethyl acetate, 3:1) gave **2** as a pale yellow oil (1.25 g, 70%): ^{1}H NMR ($CDCl_3$) δ 1.5–1.7 (m, 2 H), 1.9 (m, 1 H), 2.2 (m, 1 H), 2.6–2.8 (m, 2 H), 3.16 (dd, J = 9 Hz, J = 7 Hz, 1 H), 3.31 (s, 3 H), 3.43 (dd, J = 9 Hz, J = 4.3 Hz, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.85 (d, J = 13 Hz, 1 H), 4.20 (d, J = 13 Hz, 1 H), 6.85 (dd, J = 8 Hz, J = 1 Hz, 1 H), 7.1–7.3 (m, 2 H); IR (CH_2Cl_2) 1070, 1280, 1585, 1730 cm^{-1}; CIMS, m/z (relative intensity) 294 (M^+ + 1, 100).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90. Found: C, 65.31; H, 7.93.

(2′*S*,3*S*)-3-Carbomethoxy-1-methoxy-2-[[2′-(methoxymethyl)-pyrrolidinyl]methyl]-3-methyl-1,4-cyclohexadiene (3a). General Procedure for the Birch Reduction–Alkylation of 2. A solution of **1** (200 mg, 0.68 mmol) in dry THF (5 mL) and *tert*-butyl alcohol (51 mg, 0.68 mmol) was cooled to −78 °C, and liquid ammonia (30 mL) was added. Lithium (10 mg, 0.15 mmol) was added in small pieces, and the resulting blue solution was stirred for 20 min. The excess lithium was consumed with 1,3-pentadiene (10 μL) to give a yellow colored solution of enolate **12**.

Procedure I. Methyl iodide (87 μL, 1.3 mmol) was added at −78 °C and the mixture stirred for 30 min. After addition of saturated ammonium chloride solution (5 mL), the ammonia was removed by slow evaporation and the resulting mixture partitioned between ether and water. The aqueous layer was washed with ether (50 mL), and the combined organic extracts were washed with brine (50 mL) and dried over anhydrous potassium carbonate. The solvent was removed to give a yellow oil (^{1}H NMR analysis; 13:1 mixture of diastereomers). Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3a** as a pale yellow oil (188 mg, 89%, 13:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.60 (m, 3 H), 1.85 (m, 1 H), 2.30 (m, 1 H), 2.61 (m, 1 H), 2.88 (m, 3 H), 3.10 (dd, J = 9 Hz, J = 8 Hz, 1 H), 3.20 (d, J = 13 Hz, 1 H), 3.24 (d, J = 13 Hz, 1 H), 3.31 (s, 3 H), 3.40 (dd, J = 9 Hz, J = 4 Hz, 1 H), 3.53 (s, 3 H), 3.61 (s, 3 H), 5.51 [apparent (app) dt, J = 10 Hz, J = 2 Hz, 1 H], 5.73 (app dt, J = 10 Hz, J = 2 Hz, 1 H); IR (CCl_4) 1100, 1220, 1730 cm^{-1}; CIMS, m/z (relative intensity) 310 (M^+ + 1, 100).

Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.79. Found: C, 65.84; H, 7.76.

Procedure IIa. The solution of enolate (0.26 mmol) was allowed to warm to −33 °C, and the ammonia was removed by slow evaporation. After 30 min the solution was warmed with an ice bath to 0 °C and stirred for an additional 30 min. The mixture was then cooled to −78 °C, and methyl iodide (33 μL, 0.52 mmol) was added. The resulting mixture was stirred for 30 min and then diluted with water (50 mL). The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine (50 mL). The solvent was dried over anhydrous potassium carbonate and concentrated to give a yellow oil (20:1 mixture of diastereomers). Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3a** as a pale yellow oil (66.4 mg, 83%, 20:1 mixture of diastereomers).

Procedure IIb. The solution of enolate (0.17 mmol) was allowed to warm to −33 °C, and ammonia was removed by slow evaporation. After 30 min the solution was warmed with an ice bath to 0 °C and stirred for an additional 30 min. Methyl iodide (22 μL, 0.34 mmol) was added, and the resulting mixture was stirred for 30 min. The reaction mixture was diluted with water (50 mL), and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous potassium carbonate, and concentrated to give a yellow oil (3:1 mixture of diastereomers). Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3a** as a pale yellow oil (20:1 mixture of diastereomers) and another fraction consisting of a 1:1 mixture of the diastereomers.

Minor diastereomer (isolated as 1:1 mixture of diastereomers): characteristic ^{1}H NMR ($CDCl_3$) resonances include δ 1.39 (s, 3 H), 3.29 (s, 3 H), 3.52 (s, 3 H), 3.55 (s, 3 H).

(2′*S*,3*S*)-3-Carbomethoxy-3-ethyl-1-methoxy-2-[[2′-(methoxymethyl)pyrrolidinyl]methyl]-1,4-cyclohexadiene (3b). Procedure I (EtI): ^{1}H NMR analysis; 10:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3b** as a pale yellow oil (79%, >20:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 0.72 (t, J = 7 Hz, 3 H), 1.55–1.70 (m, 4 H), 1.87 (m, 1 H), 2.13 (m, 1 H), 2.32 (m, 1 H), 2.70 (m, 1 H), 2.88 (m, 2 H), 3.13–3.23 (m, 2 H), 3.23–3.52 (m, 3 H), 3.32 (s, 3 H), 3.56 (s, 3 H), 3.61 (s, 3 H), 5.70 (app dt, J = 10 Hz, J = 2 Hz, 1 H), 5.86 (app dt, J = 10 Hz, J = 2 Hz, 1 H); IR (film) 1225, 1655, 1725 cm^{-1}; CIMS, m/z (relative intensity) 324 (M^+ + 1, 100).

Procedure IIa: ^{1}H NMR analysis; 15:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3b** as a yellow oil (84%, >20:1 mixture of diastereomers).

Procedure IIb: ^{1}H NMR analysis; 1:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3b** as a pale yellow oil (>20:1 mixture of diastereomers) and the minor diastereomer as a pale yellow oil (1:>20 mixture of diastereomers).

Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.55 (t, J = 7 Hz, 3 H), 1.35–1.75 (m, 4 H), 1.87 (m, 1 H), 2.13 (m, 2 H), 2.55 (m, 1 H), 2.75–3.2 (m, 4 H), 3.15–3.50 (m, 3 H), 3.37 (s, 3 H), 3.61 (s, 3 H), 3.63 (s, 3 H), 5.32 (app dt, J = 10 Hz, J = 2 Hz, 1 H), 5.86 (ddd, J = 10 Hz, J = 3 Hz, J = 3 Hz, 1 H); IR (film) 1220, 1670, 1730 cm^{-1}; CIMS, m/z (relative intensity) 324 (M^+ + 1, 100).

(2′*S*,3*S*)-3-Carbomethoxy-1-methoxy-2-[[2′-(methoxymethyl)-pyrrolidinyl]methyl]-3-(1-propyl)-1,4-cyclohexadiene (3c). Procedure I (*n*-PrI): ^{1}H NMR analysis; 10:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3c** as a pale yellow oil (78%, >20:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6 Hz, 3 H), 1.10 (m, 2 H), 1.50–1.70 (m, 4 H), 1.90 (m, 1 H), 2.12 (m, 1 H), 2.32 (m, 1 H), 2.68 (m, 1 H), 2.80–2.92 (m, 3 H), 3.18–3.25 (m, 2 H), 3.42–3.52 (m, 2 H), 3.35 (s, 3 H), 3.57 (s, 3 H), 3.64 (s, 3 H), 5.41 (ddd, J = 1 Hz, J = 2 Hz, J = 10 Hz, 1 H), 5.84 (app dt, J = 10 Hz, J = 2 Hz, 1 H); IR (CCl_4) 1220, 1660, 1720 cm^{-1}; CIMS, m/z (relative intensity) 338 (M^+ + 1, 100).

Procedure IIa: ^{1}H NMR analysis; 15:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3c** as a pale yellow oil (75%, >20:1 mixture of diastereomers).

Procedure IIb: ^{1}H NMR analysis; 1:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3c** as a pale yellow oil (>20:1 mixture of diastereomers) and the minor diastereomer as a pale yellow oil (1:>20 mixture of diastereomers).

Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.90–1.20 (m, 5 H), 1.40–1.70 (m, 4 H), 1.89 (m, 1 H), 2.02–2.10 (m, 2 H), 2.55 (m, 1 H), 2.75–3.05 (m, 3 H), 3.08–3.25 (m, 2 H), 3.35–3.50 (m, 2 H), 3.34 (s, 3 H), 3.55 (s, 3 H), 3.56 (s, 3 H), 5.36 (app dt, J = 10 Hz, J = 1 Hz, 1 H), 5.86 (app dt, J = 10 Hz, J = 3 Hz, 1 H); IR (CCl_4) 1220, 1658, 1720 cm^{-1}; CIMS, m/z (relative intensity) 338 (M^+ + 1, 100).

(2′*S*,3*S*)-3-Benzyl-3-carbomethoxy-1-methoxy-2-[[2′-(methoxymethyl)pyrrolidinyl]methyl]-1,4-cyclohexadiene (3d). Procedure I (BnCl): ^{1}H NMR analysis; <2:1 mixture of diastereomers. Flash chromatography (alumina, hexane–ethyl acetate, 3:1) gave the product as a pale yellow oil (73%, >2:1 mixture of diastereomers).

Procedure IIa: ^{1}H NMR analysis; <2:1 mixture of diastereomers.

Procedure IIb: ^{1}H NMR analysis; <2:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3d** as a pale yellow oil (>20:1 mixture of diastereomers) and the minor diastereomer as a pale yellow oil (1:>20 mixture of diastereomers).

Major diastereomer **3d**: ^{1}H NMR ($CDCl_3$) δ 1.50–1.65 (m, 3 H), 1.85–2.20 (m, 3 H), 2.48–2.65 (m, 2 H), 2.91 (d, J = 14 Hz, 1 H), 2.91–3.00 (m, 1 H), 3.20–3.60 (m, 5 H), 3.29 (s, 3 H), 3.43 (s, 3 H), 3.62 (s, 3 H), 5.52 (app dt, J = 10 Hz, J = 1 Hz, 1 H), 5.72 (ddd, J = 3 Hz, J = 4 Hz, J = 10 Hz, 1 H), 7.00–7.10 (m, 2 H), 7.10–7.20 (m, 3 H); IR (CCl_4) 1225, 1655, 1730 cm^{-1}; CIMS, m/z (relative intensity) 386 (M^+ + 1, 100).

Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 1.68–1.71 (m, 3 H), 1.81–2.10 (m, 2 H), 2.36–2.65 (m, 2 H), 2.75–3.10 (m, 3 H), 3.20–3.55 (m, 5 H), 3.31 (s, 3 H), 3.36 (s, 3 H), 3.65 (s, 3 H), 5.55 (app dt, J = 10 Hz, J = 1 Hz, 1 H), 5.72 (ddd, J = 10 Hz, J = 4 Hz, J = 3 Hz, 1 H), 7.02–7.25 (m, 5 H); IR (CCl_4) 1232, 1655, 1730 cm^{-1}; CIMS, m/z (relative intensity) 386 (M^+ + 1, 100).

(2′*S*,3*S*)-3-Carbomethoxy-1-methoxy-2-[[2′-(methoxymethyl)-pyrrolidinyl]methyl]-3-(2-propenyl)-1,4-cyclohexadiene (3e). Procedure I (CH_2=$CHCH_2Br$): ^{1}H NMR analysis; 1:1 mixture of diastereomers. Flash chromatography (alumina, hexane–ethyl acetate, 3:1) gave the product as a pale yellow oil (79%, 1:1 mixture of diastereomers).

Procedure IIa: ^{1}H NMR analysis; <2:1 mixture of diastereomers. Flash chromatography (alumina, hexane–ethyl acetate, 3:1) gave the product as a pale yellow oil (74%, 1:1 mixture of diastereomers).

Procedure IIb: ^{1}H NMR analysis; 1:<2 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3e** as a pale yellow oil (>20:1 mixture of diastereomers) and the minor diastereomer as a pale yellow oil (1:>20 mixture of diastereomers).

Major diastereomer **3e**: ^{1}H NMR ($CDCl_3$) δ 1.50–1.80 (m, 3 H), 1.90 (m, 1 H), 2.35 (m, 1 H), 2.50 (m, 1 H), 2.70 (m, 1 H), 2.80–3.05 (m, 3 H), 3.10–3.30 (m, 2 H), 3.30–3.55 (m, 3 H), 3.34 (s, 3 H), 3.56 (s, 3 H), 3.65 (s, 3 H), 4.95–5.10 (m, 2 H), 5.45 (app dt, J = 10 Hz, J =

1 Hz, 1 H), 5.62 (m, 1 H), 5.86 (app dt, J = 10 Hz, J = 3 Hz, 1 H). IR (CCl_4) 1230, 1655, 1735 cm^{-1}; CIMS, m/z (relative intensity) 336 ($M^+ + 1$, 100).

Minor diastereomer: ^1H NMR ($CDCl_3$) δ 1.30–1.75 (m, 3 H), 1.88 (m, 1 H), 2.10 (m, 1 H), 2.38–2.62 (m, 2 H), 2.75–3.05 (m, 3 H), 3.15–3.28 (m, 2 H), 3.45–3.50 (m, 3 H), 3.38 (s, 3 H), 3.53 (s, 3 H), 3.57 (s, 3 H), 4.95–5.10 (m, 2 H), 5.39 (app dt, J = 10 Hz, J = 2 Hz, 1 H), 5.58 (m, 1 H), 5.87 (app dt, J = 10 Hz, J = 3 Hz, 1 H); IR (CCl_4) 1225, 1655, 1730 cm^{-1}; CIMS, m/z (relative intensity) 336 ($M^+ + 1$, 100).

(2′*S*,3*S*)-3-Carbomethoxy-1-methoxy-2-[[2′-(methoxymethyl)-pyrrolidinyl]methyl]-3-(2-propynyl)-1,4-cyclohexadiene (3f). Procedure I (CH≡CCH$_2$Br): ^1H NMR analysis; 10:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3f** as a pale yellow oil (54%, >20:1 mixture of diastereomers): ^1H NMR ($CDCl_3$) δ 1.50–1.70 (m, 4 H), 1.87 (t, J = 2 Hz, 1 H), 1.90 (m, 1 H), 2.28 (m, 1 H), 2.60 (m, 1 H), 2.87 (dd, J = 7 Hz, J = 2 Hz, 1 H), 2.90–3.50 (m, 7 H), 3.34 (s, 3 H), 3.59 (s, 3 H), 3.68 (s, 3 H), 5.60 (app dt, J = 9 Hz, J = 3 Hz, 1 H), 5.97 (app dt, J = 10 Hz, J = 1 Hz, 1 H); IR (CCl_4) 1650, 1725, 2120, 3305 cm^{-1}; CIMS, m/z (relative intensity) 334 ($M^+ + 1$, 100).

Procedure IIa: ^1H NMR analysis; 20:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3f** as a pale yellow oil (50%, >20:1 mixture of diastereomers).

Procedure IIb: ^1H NMR analysis; 4:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3f** as a pale yellow oil (>20:1 mixture of diastereomers) and the minor diastereomer as a pale yellow oil (1:>20 mixture of diastereomers).

Minor diastereomer: ^1H NMR ($CDCl_3$) δ 1.50–1.70 (m, 4 H), 1.90 (m, 1 H), 2.08 (m, 1 H), 2.60 (m, 1 H), 2.70 (dd, J = 7 Hz, J = 2 Hz, 1 H), 2.90–3.50 (m, 8 H), 3.37 (s, 3 H), 3.57 (s, 3 H), 3.58 (s, 3 H), 5.52 (app dt, J = 10 Hz, J = 1 Hz, 1 H), 5.95 (app dt, J = 10 Hz, J = 2 Hz, 1 H); IR (CCl_4) 1665, 1725, 2120, 3310 cm^{-1}; CIMS, m/z (relative intensity) 334 ($M^+ + 1$, 100).

(2′*S*,3*S*)-3-Carbomethoxy-3-(cyanomethyl)-1-methoxy-2-[[2′-(methoxymethyl)pyrrolidinyl]methyl]-1,4-cyclohexadiene (3g). Procedure I (BrCH$_2$CN): ^1H NMR analysis; >20:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3g** as a pale yellow oil (63%, >20:1 mixture of diastereomers): ^1H NMR ($CDCl_3$) δ 1.5 (m, 1 H), 1.65 (m, 2 H), 1.85 (m, 2 H), 2.22 (m, 1 H), 2.56 (m, 1 H), 2.68 (d, J = 14 Hz, 1 H), 3.33 (s, 3 H), 3.40–3.90 (m, 5 H), 3.53 (d, J = 13 Hz, 1 H), 3.61 (s, 3 H), 3.71 (s, 3 H), 3.84 (d, J = 14 Hz, 1 H), 5.53 (app dt, J = 10 Hz, J = 1 Hz, 1 H), 5.84 (app dt, J = 10 Hz, J = 3 Hz, 1 H); IR (CCl_4) 1235, 1655, 1730, 2250 cm^{-1}; CIMS, m/z (relative intensity) 335 ($M^+ + 1$, 100).

Procedure IIa: ^1H NMR analysis; >20:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3g** as a pale yellow oil (54%, >20:1 mixture of diastereomers).

Procedure IIb: ^1H NMR analysis; 4:1 mixture of diastereomers. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **3b** as a pale yellow oil (4:1 mixture of diastereomers).

Minor diastereomer: characteristic ^1H NMR resonances include δ 2.88 (d, J = 14 Hz), 3.36 (s, 3 H), 3.59 (s, 3 H).

(3*S*)-3-Carbomethoxy-3-methyl-2-*exo*-methylenecyclohex-5-en-1-one (4a). A mixture of **3a** (2.10 g, 6.80 mmol) and *p*-toluenesulfonic acid monohydrate (1.42 g, 7.48 mmol) in benzene (75 mL) was heated at reflux for 2 h and then cooled to room temperature. The benzene solution was diluted with ethyl acetate (75 mL) and washed with sodium bicarbonate solution (50 mL, 10%), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give a yellow oil. The crude material was dissolved in methylene chloride (50 mL), and *m*-chloroperbenzoic acid (1.28 g, 7.48 mmol) was added. The mixture was stirred for 1 h and then diluted with methylene chloride (50 mL). The mixture was transferred to a separatory funnel and washed with sodium bicarbonate solution (50 mL, 10%), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give a yellow oil. Flash chromatography (silica gel, hexane–ethyl acetate, 10:1) gave **4a** as a colorless oil (0.95 g, 78%): ^1H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 2.38 (app dt, J = 18 Hz, J = 2 Hz, 1 H), 3.08 (dd, J = 18 Hz, J = 5 Hz, 1 H), 3.68 (s, 3 H), 5.49 (s, 1 H), 6.20 (dd, J = 10 Hz, J = 2 Hz, 1 H), 6.23 (s, 1 H), 6.97 (ddd, J = 10 Hz, J = 5 Hz, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.8, 37.2, 49.6, 52.7, 120.5, 130.0, 146.2, 147.7, 175.1, 187.6; IR (CCl_4) 1265, 1615, 1675, 1730 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 365 (tail, 22), 340 (31), 235 (5161), 210 (5479); CIMS, m/z (relative intensity) 181 ($M^+ + 1$, 100).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.71; H, 6.73. HPLC analysis indicated that **4a** had been prepared with 88% ee. $[\alpha]^{23}_D$: −66.9° (*c* 0.91, $CHCl_3$).

(3*S*)-3-Ethyl-3-carbomethoxy-2-*exo*-methylenecyclohex-5-en-1-one (4b): prepared as described for **4a**. Flash chromatography (silica gel, hexane–ethyl acetate, 10:1) gave **4b** as a colorless solid (63%), mp 34–36 °C: ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 8 Hz, 3 H), 1.83 (m, 1 H), 2.03 (m, 1 H), 2.30 (app dt, J = 18 Hz, J = 3 Hz, 1 H), 3.03 (dd, J = 18 Hz, J = 7 Hz, 1 H), 3.63 (s, 3 H), 5.46 (s, 1 H), 6.10 (d, J = 8 Hz, 1 H), 6.19 (s, 1 H), 6.95 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.9, 28.7, 33.9, 52.5, 53.8, 121.1, 129.7, 145.4, 148.4, 174.0, 187.7; IR ($CHCl_3$) 1613, 1675, 1730 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 365 (tail, 24.4), 330 (37.15), 242 (7171), 206 (2211); CIMS, m/z (relative intensity) 195 ($M^+ + 1$, 100).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.25. Found: C, 68.15; H, 7.30. HPLC analysis indicated that **4b** had been prepared with 97% ee. $[\alpha]^{20}_D$: −60.2° (*c* 0.88, $CHCl_3$).

(3*S*)-3-Carbomethoxy-2-*exo*-methylene-3-propylcyclohex-5-en-1-one (4c): prepared as described for **5a**; flash chromatography (silica gel, hexane–ethyl acetate, 10:1) gave **5c** as a colorless oil (76%): ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3 H), 1.28 (m, 2 H), 1.82 (m, 2 H), 2.35 (app dt, J = 18 Hz, J = 2 Hz, 1 H), 3.05 (dd, J = 18 Hz, J = 5 Hz, 1 H), 3.63 (s, 3 H), 5.45 (s, 1 H), 6.10 (dd, J = 12 Hz, J = 2 Hz, 1 H), 6.19 (s, 1 H), 6.95 (ddd, J = 12 Hz, J = 5 Hz, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4, 17.9, 34.4, 38.1, 52.5, 53.5, 121.0, 129.7, 145.6, 148.5, 174.2, 187.8; IR (CCl_4) 1220, 1610, 1675, 1730 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 365 (tail, 23), 343 (30), 242 (2854), 203 (7687); CIMS, m/z (relative intensity) 209 ($M^+ + 1$, 100).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74. Found: C, 69.22; H, 7.76. $[\alpha]^{28}_D$ −34.5 (*c* 1.11, $CHCl_3$).

(3*R*)-3-Benzyl-3-carbomethoxy-2-*exo*-methylenecyclohex-5-en-1-one (4d): prepared as described for **4a**. Flash chromatography (silica gel, hexane–ethyl acetate, 4:1) gave **4d** as colorless crystals (72%), mp 114 °C: ^1H NMR ($CDCl_3$) δ 2.32 (app dt, J = 18 Hz, J = 2 Hz, 1 H), 2.83 (dd, J = 18 Hz, J = 6 Hz, 1 H), 2.97 (d, J = 14 Hz, 1 H), 3.43 (d, J = 14 Hz, 1 H), 3.68 (s, 3 H), 5.62 (s, 1 H), 6.14 (d, J = 8 Hz, 1 H), 6.32 (s, 1 H), 6.93 (m, 1 H), 7.03 (m, 2 H), 7.21 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 33.3, 42.5, 53.1, 55.1, 122.7, 127.7, 129.0, 130.1, 130.5, 136.6, 146.1, 149.2, 173.5, 187.5; IR ($CHCl_3$) 1605, 1670, 1725, 2960, 3015; UV (Et_2O) λ_{max} (ϵ) 365 (42), 360 (43), 238 (10158), 213 (13963); CIMS, m/z (relative intensity) 257 ($M^+ + 1$, 100).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.01; H, 6.34.

(3*S*)-3-Carbomethoxy-2-*exo*-methylene-3-(2-propenyl)cyclohex-5-en-1-one (4e): prepared as described for **4a**. Flash chromatography (silica gel, hexane–ethyl acetate, 5:1) gave **4e** and **6** (1:1 mixture, 61%): ^1H NMR ($CDCl_3$) δ 2.37 (app dt, J = 18 Hz, J = 3 Hz, 1 H), 2.53 (dd, J = 14 Hz, J = 8 Hz, 1 H), 2.72 (dd, J = 14 Hz, J = 8 Hz, 1 H), 2.97 (dd, J = 18 Hz, J = 6 Hz, 1 H), 3.65 (s, 3 H), 5.09 (m, 2 H), 5.50 (s, 1 H), 5.70 (m, 1 H), 6.12 (d, J = 10 Hz, 1 H), 6.24 (s, 1 H), 6.94 (m, 1 H).

Methyl 2-(3-Butenyl)-3-hydroxybenzoate (6). A solution of **4e** (1:1 mixture of **4e** and **6**) in chloroform was refluxed for 1 h. Flash chromatography (silica gel, hexane–ethyl acetate, 5:1) gave **6** as a colorless solid, mp 46–48 °C: ^1H NMR ($CDCl_3$) δ 2.50 (dt, J = 8 Hz, J = 8 Hz, 2 H), 3.15 (t, J = 8 Hz, 2 H), 4.02 (s, 3 H), 5.15 (m, 2 H), 5.39 (br s, 1 H), 6.05 (m, 1 H), 7.05 (d, J = 8 Hz, 1 H), 7.21 (app dt, J = 8 Hz, 1 H), 7.52 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.5, 33.9, 52.0, 115.0, 118.8, 122.9, 126.6, 129.4, 131.7, 138.5, 154.1, 168.3; IR ($CHCl_3$) 1700, 3010, 3410 (br), 3600 cm^{-1}; CIMS, m/z (relative intensity) 207 (100).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.56; H, 6.79.

(3*R*)-Carbomethoxy-2-*exo*-methylene-3-(2-propynyl)cyclohex-5-en-1-one (4f): prepared as described for **4a**. Flash chromatography (silica gel, hexane–ethyl acetate, 5:1) gave **4f** as a colorless oil (71%): ^1H NMR ($CDCl_3$) δ 2.11 (t, J = 2 Hz, 1 H), 2.75 (app dt, J = 18 Hz, J = 3 Hz, 1 H), 2.78 (m, 2 H), 3.05 (dd, J = 18 Hz, J = 5 Hz, 1 H), 3.69 (s, 3 H), 5.57 (s, 1 H), 6.15 (d, J = 10 Hz, 1 H), 6.30 (s, 1 H), 6.96 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.1, 33.8, 52.8, 52.9, 72.7, 79.0, 122.5, 129.7, 143.1, 147.4, 172.9, 186.5; IR (film) 1600, 1665, 1725, 2110, 2950, 3290 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 365 (tail, 27.1), 340 (41.0), 240 (6761), 207 (4376); CIMS, m/z (relative intensity) 205 ($M^+ + 1$, 100).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93. Found: C, 70.53; H, 6.06. $[\alpha]^{24}_D$: −34.3° (*c* 0.74, $CHCl_3$).

(3*R*)-3-Carbomethoxy-3-(cyanomethyl)-2-*exo*-methylenecyclohex-5-en-1-one (4g): prepared as described for **4a**. Flash chromatography (silica gel, hexane–ethyl acetate, 3:1) gave **4g** as a colorless oil (57%): ^1H NMR ($CDCl_3$) δ 2.73 (ddd, J = 18 Hz, J = 2 Hz, J = 1 Hz, 1 H), 2.90 (d, J = 19 Hz, 1 H), 2.98 (d, J = 19 Hz, 1 H), 3.14 (ddd, J = 18 Hz, J = 4 Hz, J = 1 Hz, 1 H), 3.76 (s, 3 H), 5.48 (s, 1 H), 6.22 (d, J = 10 Hz, 1 H), 6.37 (s, 1 H), 6.94 (ddd, J = 10 Hz, J = 4 Hz, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.1, 33.6, 51.2, 53.5, 116.1, 123.4, 129.9, 141.6, 145.7, 171.5, 184.7; IR (film) 1600, 1665, 1725, 2240,

2950, 3025 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 365 (tail, 23.2), 343 (30.8), 242 (7688), 203 (2854); CIMS, m/z (relative intensity) 206 ($M^+ + 1$, 100).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.31; H, 5.29. HPLC analysis indicated that **4g** had been prepared in 91% ee. $[\alpha]^{26}_D$: −23.2° (c 1.04, $CHCl_3$).

Trityl Chloride Reaction 1. A solution of **2** (85 mg, 0.29 mmol) in dry THF (2 mL) and *tert*-butyl alcohol (21 mg, 0.29 mmol) was cooled to −78 °C, and liquid ammonia (20 mL) was added. Lithium (10 mg, 0.15 mmol) was added in small pieces, and the resulting blue solution was stirred for 20 min. The excess lithium was consumed with 1,3-pentadiene (5 μL) to give a yellow solution of enolate. Trityl chloride (80 mg, 0.44 mmol) was added, and the resulting mixture was allowed to warm to room temperature. The reaction mixture was partitioned between ether and water. The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine (50 mL). The solvent was dried over anhydrous potassium carbonate and concentrated to give a mixture of triphenylmethane and **2** (^{1}H NMR analysis).

Trityl Chloride Reaction 2. A solution of **2** (85 mg, 0.29 mmol) in dry THF (2 mL) and *tert*-butyl alcohol (21 mg, 0.29 mmol) was cooled to −78 °C, and liquid ammonia (20 mL) was added. Lithium (10 mg, 0.15 mmol) was added in small pieces, and the resulting blue solution was stirred for 20 min. The excess lithium was consumed with 1,3-pentadiene (5 μL) to give a yellow solution of enolate. Trityl chloride (80 mg, 0.44 mmol) was added, and the resulting mixture was stirred at −78 °C for 30 min. Methyl iodide (48 mg, 0.34 mmol) was then added, and the mixture was allowed to warm to room temperature. The reaction mixture was partitioned between ether and water. The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine (50 mL). The solution was dried over anhydrous potassium carbonate and concentrated to give a mixture of trityl chloride and **3a** (^{1}H NMR analysis, 13:1 ratio of diastereomers).

Competition Study between Methyl Iodide and *n*-Propyl Iodide. A solution of **2** (200 mg, 0.170 mmol) in dry THF (2 mL) and *tert*-butyl alcohol (13 mg, 0.17 mmol) was cooled to −78 °C, and liquid ammonia (20 mL) was added. Lithium (3 mg, 0.40 mmol) was added in small pieces, and the resulting blue solution was stirred for 20 min. The excess lithium was consumed with 1,3-pentadiene (5 μL) to give a yellow solution of enolate. At this time, a mixture of methyl iodide (0.17 mmol) and *n*-propyl iodide (0.17 mmol) was added as a THF solution (1 mL) and the resulting mixture stirred at −78 °C for 30 min. After addition of saturated ammonium chloride solution (5 mL), the ammonia was removed by slow evaporation and the resulting mixture partitioned between ether and water. The aqueous extracts were washed with brine (50 mL) and dried over anhydrous potassium carbonate. Concentration gave a yellow oil (**3a**:**3c**, >10:1; ^{1}H NMR and GC analysis). The ratio of **3a** and its diastereomer was 13:1 (^{1}H NMR analysis).

Competition study between methyl iodide and allyl bromide: 3a:3e, 1:1.5, ^{1}H NMR and GC analysis; **3a** 13:1, **3e** 1:1, ^{1}H NMR analysis.

Competition study between methyl iodide and benzyl bromide: 3a:3d, 1:4, ^{1}H NMR and GC analysis; **3a** 13:1, **3d** 1:1, ^{1}H NMR analysis.

Competition study between methyl iodide and propargyl bromide: 3a:3f, 1:1.8, ^{1}H NMR and GC analysis; **3a** 13:1, **3f** >20:1, ^{1}H NMR analysis.

Hydrogenation of 3f. A solution of **3f** (25 mg, 0.07 mmol) in benzene (5 mL) and 5% Pd on $BaSO_4$ (5 mg) was stirred under an atmosphere of hydrogen for 15 min. The mixture was then filtered through cotton and concentrated to give a mixture of **3c** and **3e** (1:1, ^{1}H NMR analysis).

(2*R*,3*S*)-3-Carbomethoxy-2,3-dimethylcyclohexan-1-one (7). To a solution of **4a** (850 mg, 4.72 mmol) in dry methylene chloride (100 mL) was added $[Ir(cod)(py)PCy_3]PF_6$ (180 mg, 5 mol %). The mixture was stirred under an atmosphere of hydrogen for 4 h and then concentrated. The residue was dissolved in ether and filtered through a cotton plug to remove the insoluble materials. The solution was concentrated and the residue dissolved in ethyl acetate (100 mL). Rh on alumina (5%, 50 mg) was added, and the mixture was stirred under an atmosphere of hydrogen for an additional 3 h. The mixture was concentrated to give a yellow oil (14:1 mixture of diastereomers; ^{1}H NMR analysis). Flash chromatography (silica gel, hexane–ethyl acetate, 7:1) gave **7** (731 mg, 84%): ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7 Hz, 3 H), 1.01 (s, 3 H), 1.60–2.40 (m, 6 H), 2.95 (q, J = 7 Hz, 1 H), 3.69 (s, 3 H); IR (film) 1430, 1710, 1730, 2970 cm^{-1}; CIMS, m/z (relative intensity) 185 ($M^+ + 1$, 100).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.30; H, 8.79. $[\alpha]^{25}_D$: +36° (c 1.79, $CHCl_3$).

Minor diastereomer (51 mg, 6%): ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 7 Hz, 3 H), 1.30 (s, 3 H), 1.70–1.90 (m, 3 H), 2.00–2.35 (m, 2 H), 2.21 (q, J = 7 Hz, 1 H), 2.41–2.52 (m, 1 H), 3.62 (s, 3 H); IR (film) 1440, 1710, 1730, 2980 cm^{-1}; CIMS, m/z (relative intensity) 185 ($M^+ + 1$, 100).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.11; H, 8.76.

(1*S*,2*R*,3*S*)-3-Carbomethoxy-2,3-dimethyl-1-hydroxycyclohexane (8). A solution of **7** (800 mg, 4.35 mmol) in ethanol (100 mL) was cooled to 0 °C, and $NaBH_4$ (248 mg, 6.52 mmol) was added in portions. The mixture was stirred at 0 °C for 2 h, after which saturated ammonium chloride solution (10 mL) was added. The mixture was stirred for 1 h and concentrated. The residue was dissolved in water (100 mL) and extracted with ether (3 × 75 mL). The combined organic extracts were washed with brine (75 mL) and dried over anhydrous Na_2SO_4. The solvent was removed, and flash chromatography of the residue (silica gel, hexane–ethyl acetate, 5:1) gave **8** as a single diastereomer (782 mg, 97%): ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7 Hz, 3 H), 1.17 (s, 3 H), 1.30–1.90 (m, 7 H), 2.36 (m, 1 H), 3.68 (s, 3 H), 3.71 (m, 1 H); IR (neat) 1450, 1720, 2960, 3450 (br) cm^{-1}; CIMS, m/z (relative intensity) 187 ($M^+ + 1$, 89), 169 ($M^+ + 1 - H_2O$, 100).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.41; H, 9.67. $[\alpha]^{26}_D$: −21.1° (c 1.14, $CHCl_3$).

(1*S*,2*S*)-1-Carbomethoxy-1,2-dimethylcyclohexane (9). To a solution of **8** (220 mg, 1.18 mmol) in benzene (50 mL) were added Celite (3 g) and P_2O_5 (2.0 g, 14 mmol). The mixture was stirred under a nitrogen atmosphere for 18 h, then diluted with ether (100 mL), and filtered through a cotton plug. The organic layer was washed with sodium bicarbonate solution (10%, 1 × 75 mL) and brine (75 mL) and dried over anhydrous sodium sulfate. The solvent was carefully removed until only a few milliliters remained. The remainder of solvent was removed by a stream of nitrogen to give a pale yellow oil (162 mg, 82%): ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.53–1.73 (m, 6 H), 2.01–2.11 (m, 3 H), 3.69 (s, 3 H), 5.55 (m, 1 H); IR (film) 1440, 1730, 2950 cm^{-1}; CIMS, m/z (relative intensity) 169 ($M^+ + 1$, 100). The crude oil was dissolved in methylene chloride (100 mL), and $[Ir(cod)(py)PCy_3]PF_6$ (143 mg, 5 mol %) was added. The solution was stirred for 12 h under an atmosphere of hydrogen and then concentrated. The residue was dissolved in ether, and flash chromatography (silica gel, diethyl ether) gave **9** as a pale yellow oil (527 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 0.77 (d, J = 7 Hz, 3 H), 1.07 (s, 3 H), 1.10–1.80 (m, 8 H), 2.00 (m, 1 H), 3.66 (s, 3 H); IR (neat) 1450, 1730, 2880, 2960 cm^{-1}; CIMS, m/z (relative intensity) 171 ($M^+ + 1$, 100).

(1*S*,2*S*)-1,2-Dimethyl-1-acetylcyclohexane (10). **9** (225 mg, 1.32 mmol) was dissolved in methanol (150 mL) and water (10 mL). Potassium hydroxide (740 mg, 13.2 mmol) was added, and the mixture was heated at reflux for 14 h. The solvent was removed and the residue dissolved in water (50 mL). The aqueous layer was washed with ether (2 × 50 mL) and neutralized with 6 N HCl. The aqueous layer was again extracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine (50 mL) and dried over anhydrous sodium sulfate. The solvent was removed to give a pale yellow oil, which solidified on standing. The crude carboxylic acid was dissolved in THF (20 mL) and cooled to 0 °C. Methyllithium (2.5 mL, 1 M) was added and the mixture stirred for 18 h. Solid NH_4Cl was added, and the mixture was concentrated. The residue was dissolved in water (50 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous sodium sulfate. The solvent was removed, and flash chromatography (silica gel, hexane–ether, 10:1) gave **10** (36 mg, 18%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.66 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 1.10–1.68 (m, 8 H), 1.94 (m, 1 H), 2.08 (s, 3 H); CIMS, m/z (relative intensity) 155 ($M^+ + 1$, 100); $[\alpha]^{27}_D$ +7.62° (c 3.66, $CHCl_3$).

(1*S*,3*S*)-3-Carbomethoxy-3-methyl-2-*exo*-methylene-1-hydroxycyclohex-5-ene (11). To a solution of **4a** (80 mg, 0.44 mmol, 96% ee) in ethanol (15 mL) was added $CeCl_3 \cdot 7H_2O$ (145 mg, 0.44 mmol). The mixture cooled to 0 °C, $NaBH_4$ (64 mg, 0.44 mmol) was added, and the mixture was stirred for 1 h. Solid NH_4Cl was added, and the mixture stirred for an additional 30 min. The solution was then concentrated and the residue partitioned between ether and water. The combined organic extracts were washed with brine (50 mL) and dried over anhydrous sodium sulfate. The solvent was removed, and flash chromatography (silica gel, hexane–ethyl acetate, 4:1) gave **11** (46 mg, 56%) as a colorless solid (mp 67–69 °C). In a subsequent larger-scale experiment, an 89% yield was obtained for this reaction: ^{1}H NMR ($CDCl_3$) 14:1 mixture of diastereomers δ 1.41 (s, 3 H), 1.65 (br s, 1 H), 1.97 (ddd, J = 17 Hz, J = 5 Hz, J = 2 Hz, 1 H), 2.81 (dd, J = 17 Hz, J = 5 Hz, 1 H), 3.65 (s, 3 H), 4.76 (br s, 1 H), 5.13 (d, J = 2 Hz, 1 H), 5.40 (d, J = 2 Hz, 1 H), 5.65 (app dt, J = 10 Hz, J = 2 Hz, 1 H), 5.75 (dm, J = 10 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 23.4, 37.8, 48.7, 52.4, 68.4, 107.5, 128.1, 130.1, 149.8, 176.0; IR (CCl_4) 1735, 2960, 3020, 3500 cm^{-1}; CIMS, m/z (relative intensity) 183 ($M^+ + 1$, 20), 165 ($M^+ + 1 - H_2O$, 100).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.61; H, 7.73. [a]$^{22}_D$: −148.9°.

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Registry No. 2, 139760-48-8; **3a** (isomer 1), 139760-49-9; **3a** (isomer 2), 139760-50-2; **3b** (isomer 1), 139760-51-3; **3b** (isomer 2), 139760-52-4; **3c** (isomer 1), 139869-59-3; **3c** (isomer 2), 139869-60-6; **3d** (isomer 1), 139760-53-5; **3d** (isomer 2), 139760-54-6; **3e** (isomer 1), 139760-55-7; **3e** (isomer 2), 139760-56-8; **3f** (isomer 1), 139760-57-9; **3f** (isomer 2), 139760-58-0; **3g** (isomer 1), 139760-59-1; **3g** (isomer 2), 139760-60-4; **4a**, 139760-61-5; **4b**, 139760-62-6; **4c**, 139760-63-7; **4d**, 139760-64-8; **4e**, 139760-65-9; **4f**, 139760-66-0; **4g**, 139760-67-1; **6**, 139760-68-2; (2*R*,3*S*)-**7**, 139894-31-8; (2*S*,3*S*)-**7**, 139894-32-9; **8**, 139760-69-3; **9**, 139894-33-0; **10**, 115588-50-6; (1*S*,3*S*)-**11**, 139760-70-6; (1*R*,3*S*)-**11**, 139894-34-1; **12**, 139760-71-7; methyl 3-methoxy-2-methylbenzoate, 42981-93-1; (*S*)-2-(methoxymethyl)pyrrolidine, 63126-47-6.

Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for the *p*-bromobenzoate derivative of **11** (7 pages). Ordering information is given on any current masthead page.

Synthesis and Aggregation Properties of a New Family of Amphiphiles with an Unusual Headgroup Topology

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Abstract: A new family of amphiphiles, derived from a rigid dicarboxylic acid headgroup unit of unusual topology, has been synthesized. The aggregation of these molecules in aqueous solution has been examined by ^{1}H NMR and dye solubilization methods. Two modes of aggregation appear to be operative within this group of amphiphiles, one determined by the headgroup and the other determined by the flexible tail. The former mode is dominant when the tail is short or nonexistent, and the latter is dominant when the tail contains six or more nonpolar atoms. The latter mode appears to be a typical micellization process, but the former is less cooperative. For the latter group of amphiphiles, comparison with literature data for a family of long chain alkyl malonate surfactants indicates that the wide, rigid headgroup, containing 10 non-carboxylate carbon atoms, has the equivalent "hydrophobic impact" on aggregation of only five CH_2 groups in the flexible tail.

Introduction

Physical studies of synthetic amphiphiles have tended to focus on molecules with a single topology: a compact polar headgroup connected to one or more flexible hydrocarbon tails.[1] This structural family is widely represented among the biologically and industrially important amphiphiles, but many other amphiphilic architectures are possible. Mukerjee, for example, has identified several structural classes of molecules that can undergo "hydrophobic association" in aqueous solution:[2] (1) species with the classical polar headgroup/nonpolar flexible tail architecture (soaps, detergents, lipids, etc.); (2) polycyclic aromatic amphiphiles that are rigid and planar (e.g., methylene blue); (3) rigid but nonplanar structures with surfaces of differing polarity (e.g., the bile acid salts); and (4) macromolecules, including proteins.

Differing aggregation behavior among these types of structures makes it clear that amphiphilic topology has a profound effect on solution behavior. Amphiphiles in the large first class tend to form discretely sized aggregates, such as micelles and vesicles.[1] Molecules in the second class, however, tend to undergo stepwise association that does not result in aggregates of discrete sizes.[3] Cholate and other steroidal members of the third class exhibit aggregation properties intermediate between those of the first two classes, showing weak cooperativity that leads to polydispersity in aggregate size.[4] Israelachvili has analyzed the effects of structural variations among species bearing a polar headgroup and at least one flexible nonpolar tail, showing that geometric packing considerations lead to a rational correlation between molecular structure and the type of aggregate formed (e.g., spherical micelles vs rod-shaped micelles vs bilayers).[5] In light of the important functions performed by amphiphilic species in diverse settings,[1] it is not surprising that exploration of new amphiphilic architectures is a subject of continuing interest.[6-11]

We are interested in an amphiphile topology that has not previously received much attention in synthetic systems: rigid structures with two discrete faces, one of which is polar and the other nonpolar. The bile salts, which possess unusual aggregation, solubilization, and membrane-modification properties,[4] have a related architecture; one face of the rigid steroid skeleton is polar, because of the hydroxyl groups, and the other is nonpolar. The bile salts differ somewhat from our structural prescription, how-

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