Synthesis of Tetrahydrolipstatin

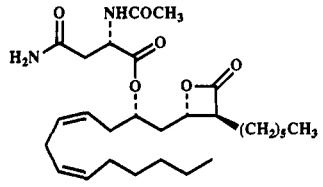
N. K. Chadha, A. D. Batcho, P. C. Tang, L. F. Courtney, C. M. Cook, P. M. Wovkulich, and M. R. Uskoković*

Roche Research Center, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

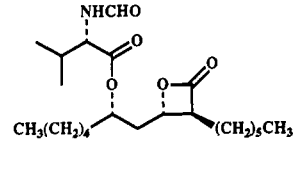
Received December 19, 1990

An asymmetric synthesis of tetrahydrolipstatin (4) is described. Application of our previously described in situ cyclopentadiene alkylation-asymmetric hydroboration protocol provided the key chiral alcohol 9. In the course of this work, the presence of a free hydroxyl group was found to exert a strong directing effect on the regioselectivity of a Baeyer-Villiger reaction (16 → 17). Subsequent transformations of lactone 17 produced tetrahydrolipstatin (4).

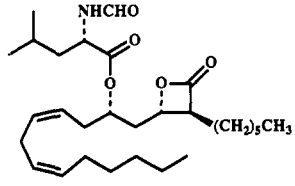
Several novel β-lactones of microbial origin exhibit useful pharmacological activities. Among them, esterastin (1),[1] isolated from *Streptomyces lavendulae* MD4-C1, valilactone (2),[2] produced by *S. albolongus* MG147-CF2, and lipstatin (3),[3a,b] obtained from *S. toxytricini*, are all inhibitors of pancreatic lipases. Tetrahydrolipstatin (4), a saturated derivative of lipstatin (3), is currently under evaluation as an antiobesity agent.[4]



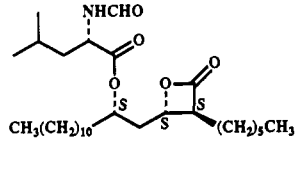
1 Esterastin



2 Valilactone

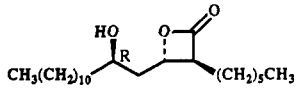


3 Lipstatin

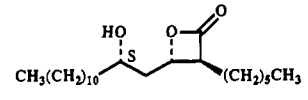


4 Tetrahydrolipstatin

Common to these natural products is the β-lactone moiety of a 5-substituted-3,5-dihydroxy-2-hexylpentanoic acid having the *SSS* absolute configuration. In the previously published syntheses of tetrahydrolipstatin (4), the *S* configuration at C_5 was established by inversion of the 5(*R*)-hydroxy β-lactone precursor **5** with *N*-formylleucine (6) under Mitsunobu conditions.[5-7] In this paper, we disclose a new asymmetric total synthesis of tetrahydrolipstatin (4) via the 5(*S*)-hydroxy β-lactone **7**.[8]



5



7

The initial target in our synthesis was hydroxy δ-lactone **17**, which corresponds to the same absolute configuration as the β-lactone **7**. The synthesis started from cyclopentadiene (8), which was alkylated via the sodium anion with hexyl iodide (Scheme I). The alkylation product was subjected to an in situ[9] asymmetric hydroboration using (+)-diisopinocampheylborane to give, after hydrogen peroxide oxidation, (1*R*,2*R*)-2-hexyl-3-cyclopenten-1-ol (**9**, 96% ee) in 57% yield overall. Inversion of configuration under Mitsunobu conditions generated the *cis*-cyclopentenol **11**. As would be eventually uncovered, the hydroxyl group of **11**, which is now in the correct absolute configuration for tetrahydrolipstatin, is a critical directing element required for the smooth introduction of the remaining structural features. The hydroxyl-directed epoxidation with *m*-CPBA provided the all-cis epoxide **12**, which, following silylation with *tert*-butyldimethylsilyl chloride, underwent a regioselective epoxide opening with the cuprate reagent derived from undecanyllithium to produce **14**. Oxidation under Swern conditions to ketone **15** proceeded uneventfully.

Next, our plan called for the use of a Baeyer-Villiger oxidation to introduce the C-O bond in **17**. Although the Baeyer-Villiger reaction of simple 2,5-disubstituted cyclopentanones was unlikely to show any useful regioselectivity, the presence of an oxygen at a β-carbon might, because of its electron-withdrawing ability, tend to disfavor the undesired migration of the adjacent carbon without affecting the desired bond migration. Unfortunately, the silyloxy ketone **15** proved to be quite resistant to the usual oxidation conditions and gave no lactone products. In dramatic contrast, however, is the behavior of the corresponding hydroxy ketone **16**. To our delight, treatment of **16** with *m*-CPBA provided a single δ-lactone, **17**, having the desired *SSS* stereochemistry.

The regioselectivity of Baeyer-Villiger reactions has been rationalized in terms of conformational,[10] stereoelectronic,[11] inductive, and strain effects.[12] Among the early conformation-based analyses is one offered by Murray to explain the preference for the migration of the bridgehead carbon in camphor over the methylene carbon. This result was interpreted as the preference for a lower energy chair transition state resulting from migration of the bridgehead carbon vs boat transition state for migration of the methylene carbon.[13] Seeking an explanation for the high

(1) Umezawa, H.; Aoyagi, T.; Hazato, T.; Uotani, K.; Kojima, F.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1978**, *31*, 639. Umezawa, H. *Ibid.* **1978**, *31*, 797.

(2) Kitahara, M.; Asano, M.; Naganawa, H.; Maeda, K.; Hamada, M.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1987**, *40*, 1647-1650.

(3) (a) Weibel, E. K., Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081. (b) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadal, Y.; Schmidt, K. *Ibid.* **1987**, *40*, 1086.

(4) The inhibition of intestinal absorption of dietary triglycerides by tetrahydrolipstatin is attributed to the inhibition of pancreatic lipases. Hogan, S.; Fleury, A.; Hadvary, P.; Lengsfeld, H.; Meier, M. K.; Triscari, J.; Sullivan, A. C. *Int. J. Obes.* **1987**, *11*, 35 (Suppl. 3).

(5) (a) Barbier, P.; Schneider, F. *Helv. Chim. Acta* **1987**, *70*, 196; (b) Barbier, P.; Schneider, F.; Widmer, U. *Ibid.* **1987**, *70*, 1412.

(6) Barbier, P., Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218.

(7) Pons, J.-M., Kocienski, P. *Tetrahedron Lett.* **1989**, *30*, 1833.

(8) After completion of this work, Fleming et al. disclosed their synthesis of 4 via 7., Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1990**, *31*, 3645.

(9) Partridge, J. J.; Chadha, N. K.; Uskoković, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. Partridge, J. J.; Chadha, N. K.; Uskoković, M. *Org. Syn.* **1985**, *63*, 44.

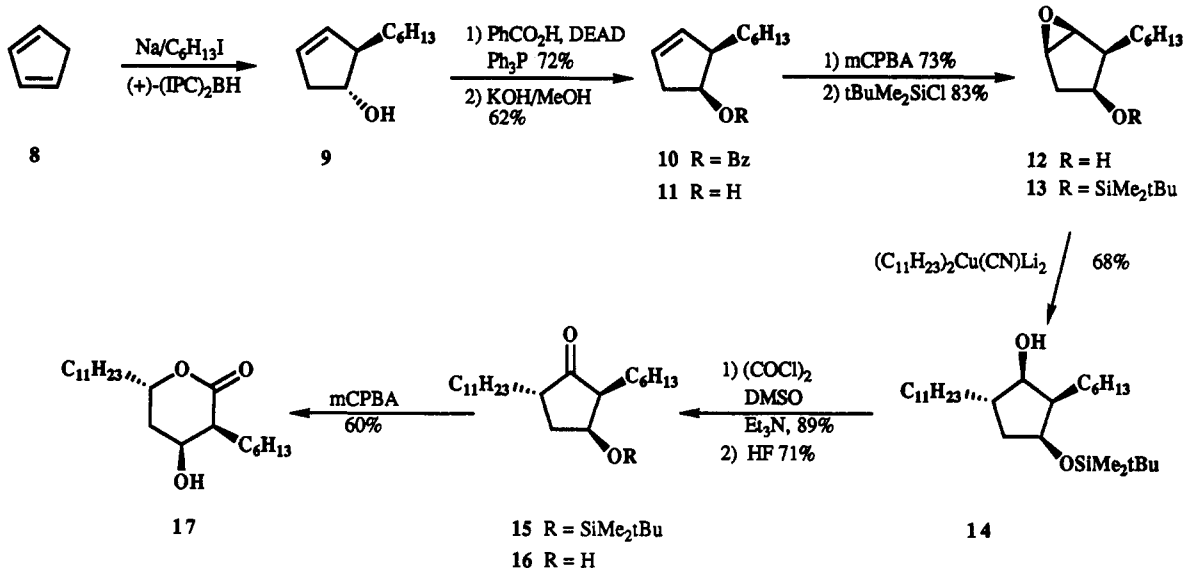
(10) Murray, M. F.; Johnson, B. A.; Pederson, R. L.; Ott, A. C. *J. Am. Chem. Soc.*, **1956**, *78*, 981. See also Sauers, R. R. *Ibid.* **1959**, *81*, 925. Meinwald, J.; Frauenglass, E. *Ibid.* **1960**, *82*, 5235. Sauers, R. R.; Ahearn, G. P. *Ibid.* **1961**, *83*, 2759.

(11) Noyori, R.; Sato, T.; Kobayshi, H. *Tetrahedron Lett.* **1980**, *21*, 2569.

(12) For a review covering Baeyer-Villiger reactions in bridged bicyclic systems in which these aspects are addressed, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697.

0022-3263/91/1956-4714$02.50/0

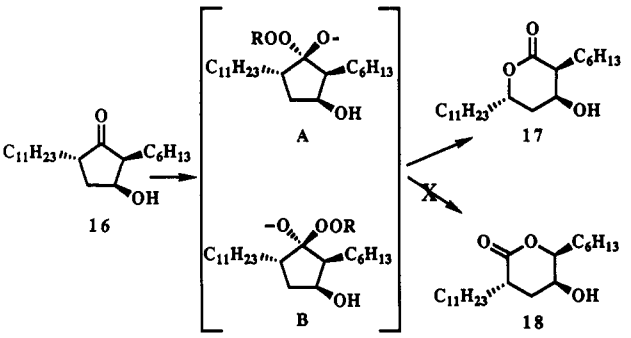
Scheme I



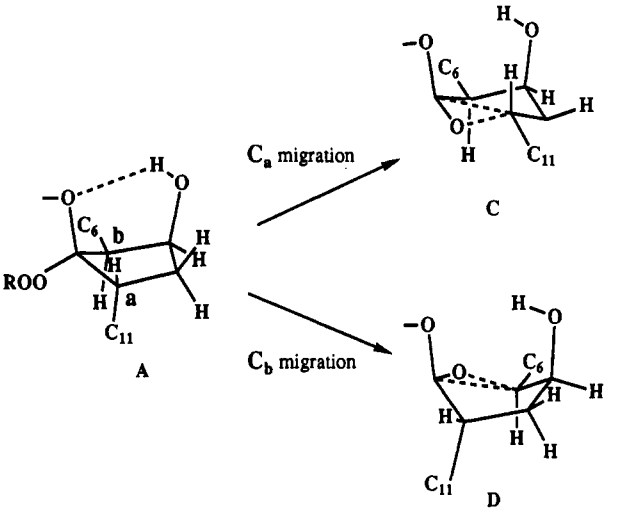
degree of regioselectivity displayed in the Baeyer–Villiger reaction of ketone **16** to form lactone **17**, the reaction was analyzed in terms of the peroxy intermediates A and B, giving consideration to the conformations of the cyclopentane rings, the peroxy groups,[11] and the six-membered rings being formed[10] (Scheme II). The calculations suggested that an oxyanion such as A would receive ca. 3.9 kcal/mol of stabilization relative to the oxyanion B through hydrogen bonding of the free hydroxyl proton to the negative oxygen. In this low-energy conformation, migration of the carbon bearing the C_{11} side chain (i.e., C_a of A) would proceed through a chairlike transition state (C), while migration of the carbon bearing the C_6 side chain (i.e., C_b of A) to form **18** would proceed via a twist-boatlike transition state (D) (Scheme III).[14]

Since the desired contrathermodynamic conversion of the δ-lactone **17** to the β-lactone **7** could not be accomplished in a single isomerization process, recourse was made to a blocking–deblocking strategy. The silyloxy δ-lactone **20**, prepared in 90% yield from **17** under standard conditions, was transformed to the ring-opened benzyl ester **21** by treatment with potassium hydroxide and benzyl bromide (Scheme IV). The 5-hydroxy group was then benzylated with *O*-benzyl trichloroacetimidate and the resulting ether **22** converted to the β-hdyroxy acid **24** via a two-step deblocking sequence. On exposure to benzenesulfonyl chloride, acid **24** cyclized to benzyloxy β-lactone **25**. Hydrogenolysis of the benzyl group in the presence of palladium on carbon gave hydroxy β-lactone

Scheme II

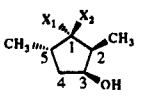


Scheme III



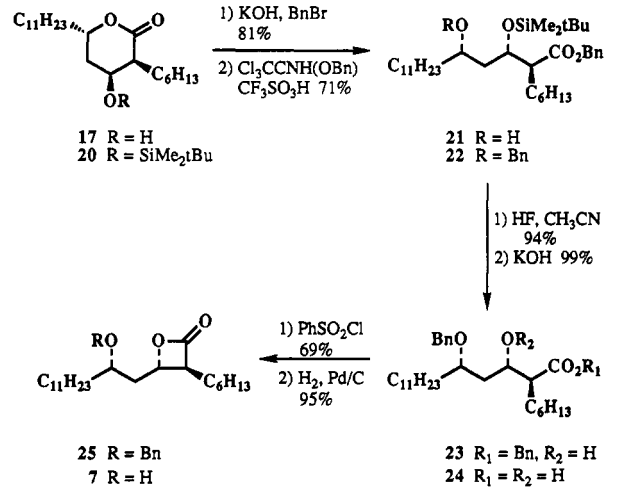
(13) One peroxy intermediate isomer was considered in that case, see ref 10.

(14) Initial examinations focused on the conformational aspects of the simplified structures **19a–c**. Conformational searches employing molecular mechanics calculations (MM2 as implemented in the program MODEL Version KS2.94) produced results that suggested the correct direction of bond migration but seriously underestimated the magnitude of the preference. To analyze the system further, particularly in regard to the participation of the free hydroxyl group in hydrogen bonded arrangements, recourse was made to *ab initio* calculations, which generally provide a better treatment of hydrogen bonding than MM2. Using the program GAUSSIAN 88, minimal basis set (STO-3G) calculations were performed on a set of ten basic envelope ring puckers of **19a**. The lowest energy structure had C_2 puckered down with hydrogen bonding from the C_3 OH to the C_1 oxygen. The next lowest energy conformer (1 kcal/mol higher in energy) had the same ring pucker but with the C_1 OH hydrogen bonded to the C_3 oxygen. At 2.7 kcal/mol higher in energy was the next conformation with the C_3 up pucker and C_1 OH hydrogen bonded to the C_3 oxygen. Calculations were then performed on the oxyanions **19d** and **19e** as closer models for the intermediates A and B, respectively. Here, only a single ring pucker corresponding to the lowest energy ring conformer of **19a** (i.e., C_2 puckered down) was used in the calulations due the length of the computation. The extended 3-21G basis set was used in the minimizations for **19d** and **19e**. In this conformation, **19d** with the oxyanion *cis* to the C_3 OH, is 3.9 kcal/mol lower in energy than the **19e**, with the oxyanion *trans* to the C_3 OH. Additional calculations at higher basis sets, which are beyond the scope of the present investigation, would be required to further quantitate the stabilization energy (see, for example: Vos, R. J.; Hendriks, R.; Van Duijneveldt, F. B. J. Comput. Chem. **1990**, *11*, 1) and to locate the transition state.



19a $R_1 = R_2 = OH$
b $R_1 = OOH$, $R_2 = OH$
c $R_1 = OH$, $R_2 = OOH$
d $R_1 = OH$, $R_2 = O^-$
e $R_1 = O^-$, $R_2 = OH$

Scheme IV



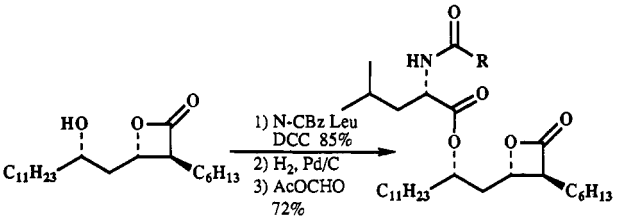
17 R = H
20 R = $SiMe_2tBu$

21 R = H
22 R = Bn

25 R = Bn
7 R = H

23 R_1 = Bn, R_2 = H
24 R_1 = R_2 = H

Scheme V



7

26 R = OBn
Tetrahydrolipstatin 4 R = H

7, which was identical with an authentic sample obtained from tetrahydrolipstatin (4).[5]

The final stage of the synthesis required the incorporation of the *N*-formylleucine group. Unfortunately, low yields thwarted attempts to accomplish this operation directly with *N*-formylleucine. Nevertheless, the coupling of 7 with the *N*-(carboxylbenzyl)-protected derivative of leucine in the presence of DCC to form ester **26** was a high-yielding process and, following hydrogenolysis and N-formylation, afforded tetrahydrolipstatin (4) in good overall yield (Scheme V).

Experimental Section

Melting points and boiling points are uncorrected. Mass spectra were determined at 70 eV. Analytical thin-layer chromatography (TLC) was performed on 0.25-mm silica gel 60-F plates (EM Reagents). Liquid chromatography was performed by using either medium-pressure (MPLC) or forced flow (flash chromatography) of the indicated solvent system on silica gel 60 (230–400 mesh; EM Reagents). Tetrahydrofuran was distilled from lithium aluminum hydride or sodium metal/benzophenone ketyl. Dichloromethane, pyridine, and dimethyl sulfoxide were stored over 4-Å molecular sieves. (−)-α-Pinene ($[\alpha^{25}]_D$ = −42° (neat)) was purchased from Aldrich Chemical Co.

(1*R*,2*R*)-2-Hexylcyclopent-3-en-1-ol (9). A solution of cyclopentadienylsodium[9] was prepared from 39.7 g (600 mmol) of cyclopentadiene in 60 mL of THF and 13.8 g (0.6 g-atom) of sodium shot in 60 mL of THF. A 100-mL portion of THF was added, and the solution was filtered through glass wool and added dropwise to a mixture of 106 g (500 mmol) of 1-iodohexane in 90 mL of THF maintained at −62 °C. To the resulting slurry was added 22.6 g (100 mmol) of hexadecane as a GC standard and the resulting mixture stirred overnight at −60 to −70 °C. The mixture was hydroborated at −78 °C with recrystallized (+)-diisopinocampheyl borane[15] prepared from 375 mL (750 mmol) of 2 M borane dimethyl sulfide complex in THF and 224.4 g (1650 mmol) of (−)-α-pinene. The solution was allowed to warm to 0 °C (ice–water) and then stirred at 0 °C for 16 h. The solution was maintained at 0 °C as 50 mL of water was added dropwise, followed by the dropwise addition of 250 mL (750 mmol) of 3 N sodium hydroxide. After 10 min, 226 mL (2200 mmol) of 30% hydrogen peroxide was added over 30 min during which time the internal temperature reached 40 °C. The cooling bath was removed, and the solution was stirred at room temperature for 4 h. The reaction mixture was diluted with 1 L of hexanes. The organic phase was separated and washed with 500 mL of 1.5 M sodium hydroxide, 500 mL of 10% sodium bisulfite, and 500 mL of water. The aqueous phases were back-extracted with 2 × 1 L of hexanes. The organic phases were combined and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 314 g of a solid. The crude product was chromatographed (5:1 hexanes/ethyl acetate) and gave 55.0 g (65%) of **9**. Distillation under reduced pressure afforded 48.3 g (57%) as a colorless oil: bp 86 °C (0.5 mm); $[\alpha]^{22}_D$ = −139.4° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 Mz; $CHCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H, CH_3), 1.2–1.4 (b m, 10 H, CH_2), 1.57 (s, 1 H, OH), 2.24 (dm, *J* = 17 Hz, 1 H), 2.69 (dm, *J* = 17 Hz, 1 H), 2.49 (b s, 1 H, allylic CH), 4.08 (b s, 1 H, CHO), 5.65 (m, 1 H), 5.68 (m, 1 H); mass spectrum *m/e* 168, 150, 139, 124, 121, 87, 67. Anal. Calcd for $C_{11}H_{20}$: C, 78.51; H, 11.98. Found: C, 78.15; H, 12.14.

The optical purity was determined to be 96% ee by NMR of the corresponding *RRS* and *RRR* MTPA[16] esters of the alcohol **9**. The C_5 allylic proton cis to the oxygen provided the diagnostic resonance and appears at δ 2.24 (dm, *J* = 17 Hz) in the alcohol **9**, δ 2.38 (dm, *J* = 18.2 Hz) in the *RRS* ester, and 2.27 (dm, *J* = 17.5 Hz) in the *RRR* ester.

(1*S*,2*R*)-2-Hexyl-3-cyclopenten-1-ol Benzoate (10). To a solution of 14.0 g (89.1 mmol) of diethyl azodicarboxylate and 10.9 g (89.1 mmol) of benzoic acid in 60 mL of anhydrous ether at 0 °C was added a solution of 23.4 g (89.1 mmol) of triphenylphosphine and 5.0 g (29.7 mmol) of **9** in 55 mL of anhydrous ether. The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered by suction and the residue washed with hexane. The filtrate was concentrated and chromatographed (30:1 hexanes/EtOAc) to give 5.88 (72%) of **10**: $[\alpha]^{22}_D$ = +14.95° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1712, 715 cm^{-1}; ^1H NMR (400 MHz) δ 0.83 (t, *J* = 7 Hz, 3H, CH_3), 1.20–1.65 (m, 10 H, CH_2), 2.49 (dm, *J* = 16 Hz, 1 H), 2.78 (dm, *J* = 16 Hz, 1 H), 2.89 (m, 1 H, allylic CH), 5.63 (dt, *J* = 3 and 6.5 Hz, 1 H, CHO), 5.77 (m, 2 H, —CH=CH—), 7.43, 7.55, 8.02 (2, 1, 2 H, Ar); mass spectrum *m/e* 272, 243, 188, 150, 105, 80, 66. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 78.84; H, 9.02.

(1*R*,2*R*)-2-Hexyl-3-cyclopenten-1-ol (11). A solution of 4.93 g (18.1 mmol) of **10** in 40 mL of 5% potassium hydroxide in methanol was heated at 50 °C for 3 h. The reaction mixture was cooled, acidified with 2 N HCl, and extracted with ether. The ether solution was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (4:1 hexanes/EtOAc) gave 1.88 g (62%) of **11**: $[\alpha]^{22}_D$ = −65.27° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3615, 3600 cm^{-1} (OH); ^1H NMR (400 MHz) δ 0.89 (t, *J* = 7 Hz, 3 H, CH_3), 1.25–1.55 (m, 10 H, CH_2), 2.32 (dm, *J* = 17 Hz, 1 H), 2.61 (dm, *J* = 17 Hz, 1 H), 2.57 (m, 1 H, allylic CH), 4.37 (m, 1 H, CHO), 5.66 (m, 1 H, —CH=C), 5.73 (m, 1 H, —CH=C); mass spectrum *m/e* 168, 150, 124, 113, 98.

(1*S*,2*S*,3*S*,5*R*)-2-Hexyl-6-oxabicyclo[3.1.0]hexan-3-ol (12). To a solution of 1.75 g (10.4 mmol) of **11** in 15 mL of anhydrous dichloromethane was added 1.76 g (21 mmol) of sodium bicarbonate and 4.51 g (21 mmol) of 80% *m*-chloroperbenzoic acid. After 2.75 h, the reaction was diluted with water and extracted with ether. The organic solution was washed with 10% sodium bisulfite, 1 N sodium hydroxide, water, and brine. The organic solution was dried ($MgSO_4$) and concentrated. The residue was chromatographed (4:1 hexane/ethyl acetate) and gave 1.4 g (73%) of **12**: $[\alpha]^{25}_D$ = −11.21° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3545 cm^{-1} (OH); ^1H NMR (400 MHz) δ 0.89 (t, *J* = 7 Hz, 3 H, CH_3), 1.25–1.70 (m, 10 H, CH_2), 1.96 (m, 1 H, CH), 1.97 (d, *J* = 15 Hz, 1 H), 2.19 (dm, *J* = 15 Hz, 1 H), 2.03 (d, *J* = 12 Hz, 1 H, OH), 3.51 (d, J_{vic} = 2 Hz, 1 H, CHO epoxide), 3.61 (d, J_{vic} = 2 Hz, 1 H, CHO

(15) Brown, H. C.; Singram, B. *J. Org. Chem.* **1984**, *49*, 944.

(16) Dale, J. A.; Mosher, H. S. J. Am. Chem. Soc. **1973**, *95*, 512.

epoxide), 3.88 (dt, J = 12, 6 Hz, 1 H, CHO). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.32; H, 10.93.

(1*S*,2*R*,3*S*,5*R*)-2-Hexyl-3-[(*tert*-butyldimethylsilyl)oxy]-6-oxabicyclo[3.1.0]hexane (13). To a solution of 1.4 g (7.6 mmol) of **12** in 10 mL of anhydrous dimethylformamide was added 2.069 g (30.4 mmol) of imidazole and 2.29 g (15.2 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was allowed to stir for 2.5 h and then quenched with water and extracted with dichloromethane. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (20:1 hexanes/EtOAc) and gave 1.88 g (83%) of **13**: $[\alpha]^{25}_D$ = −5.049° (*c*, 1.01, $CHCl_3$); IR ($CHCl_3$) 838 cm^{-1} (OSi); ^1H NMR (400 MHz) δ 0.01 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.89 (t, J = 7 Hz, 3 H, CH_3), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.25–1.60 (m, 10 H, CH_2), 1.95–2.05 (m, 3 H, ring CH_2 and CH), 3.40–3.42 (m, 2 H, epoxide), 4.19 (m, 1 H, CHO); mass spectrum m/e 299, 298, 297, 157. Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48; Si 9.4. Found: C, 68.66; H, 11.51; Si, 9.37.

(1*S*,2*S*,3*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2-hexyl-4-undecylcyclopentan-3-ol (14). To a solution of 1.89 g (8.0 mmol) of 1-bromoundecane in 100 mL of anhydrous ether at −78 °C was added 8.9 mL (15.2 mmol) of 1.7 M *tert*-butyllithium in pentane. After 40 min of stirring at −78 °C, the solution was allowed to warm to −50 °C and was stirred for 10 min. Then, 360 mg (4.0 mmol) of cuprous cyanide was added and the suspension allowed to warm to −20 °C at which time a homogeneous solution was formed. After a further 10 min, a solution of 300 mg (1 mmol) of **13** in 4 mL of ether was added and the reaction mixture was stirred at −20 °C for 2 h. The reaction was quenched by adding 25 mL of 3% ammonium hydroxide solution and the mixture extracted with ether. The ether extract was washed with water, brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (30:1 hexanes/EtOAc) and gave 310 mg (68%) of **14**: $[\alpha]^{25}_D$ = +23.83° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3115, 838 cm^{-1}; ^1H NMR (400 MHz) δ 0.06 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.88 (m, 15 H, 2 × CH_3, $SiC(CH_3)_3$), 1.15–1.65 (m, side chain CH_2), 2,89 (d, J = 11.5 Hz, 1 H, OH), 3.63 (dd, J = 4.5, 11.5 Hz, 1 H, CHO), 4.17 (m, 1 H, CHOSi); mass spectrum m/e 454, 439, 421, 411, 397, 379, 322, 305. Anal. Calcd for $C_{28}H_{58}O_2Si$: C, 73.94; H, 12.35; Si 6.17. Found: C, 74.22; H, 12.85; Si, 6.30.

(2*S*,3*S*,5*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2-hexyl-5-undecylcyclopentan-1-one (15). To a solution of 0.41 mL (4.44 mmol) of oxalyl chloride in 20 mL of dichloromethane at −50 °C was added 1.18 mL (8.88 mmol) of anhydrous dimethyl sulfoxide. A white precipitate formed upon addition, and the mixture was stirred at −50 °C for 15 min. A solution of 336 mg (0.74 mmol) of **14** in 2 mL of dichloromethane was added. After 50 min at −50 °C, 4 mL (28.7 mmol) of triethylamine was added and the mixture allowed to warm to room temperature. The reaction mixture was diluted with 10 mL of water and then extracted with dichloromethane. The organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (30:1 hexanes/EtOAc) and gave 300 mg (89%) of **15**: $[\alpha]^{25}_D$ = +113.94° (*c*, 1.09, $CHCl_3$); IR ($CHCl_3$) 1731, 838 cm^{-1}; ^1H NMR (400 MHz) δ 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.86 (t, J = 7 Hz, 3 H, CH_3), 0.88 (t, J = 7 Hz, 3 H, CH_3), 4.44 (t, 1 H, CHOSi); mass spectrum m/e 437, 409, 395, 377, 320, 297. Anal. Calcd for $C_{28}H_{56}O_2Si$: C, 74.27; H, 12.47; Si 6.20. Found: C, 74.58; H, 12.52; Si, 6.41.

(2*S*,3*S*,5*S*)-3-Hydroxy-2-hexyl-5-undecylcyclopentan-1-one (16). To a solution of 255 mg (0.56 mmol) of **15** in 60 mL of acetonitrile at 0 °C was added 2 mL of 48% hydrofluoric acid. After 5 h at room temperature, the reaction mixture was diluted with water and extracted with ether. The ether extract was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (5:1 hexanes/EtOAc) and gave 135 mg (71%) of **16**: mp 51.5 °C (hexanes); $[\alpha]^{25}_D$ = +137.7° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3615, 1732 cm^{-1}; ^1H NMR (400 MHz) δ 0.87 (t, J = 7 Hz, 3 H, CH_3), 0.88 (t, J = 7 Hz, 3 H, CH_3), 4.53 (m, 1 H, CHO); mass spectrum m/e 338, 291, 250, 166, 154, 96. Anal. Calcd for $C_{22}H_{42}O_2$: C, 78.05; H, 12.50. Found: C, 77.66; H, 12.33.

(3*S*,4*S*,6*S*)-3-Hexyl-4-hydroxy-6-undecyltetrahydro-2*H*-pyran-2-one (17). To a solution of 150 mg (0.443 mmol) of **16** in 15 mL of anhydrous dichloromethane was added 223.4 mg (2.66 mmol) of sodium bicarbonate and 572 mg (2.66 mmol) of 80% *m*-chloroperoxybenzoic acid. The mixture was stirred for 20 h and then quenched by adding dimethyl sulfide. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed (5:1 hexanes/EtOAc) and gave 94 mg (60%) of **17**: mp 105 °C (ethyl ether); $[\alpha]^{25}_D$ = −3.2° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3425, 1698 cm^{-1}; ^1H NMR (400 MHz) δ 0.88 (t, J = 7 Hz, 3 H, CH_3), 0.89 (t, J = 7 Hz, 3 H, CH_3), 1.2–1.75 (m, 32 H), 2.10 (m, 1 H, ring CH_2, equatorial), 2.31 (m, 1 H, CH), 4.29 (b s, 1 H, C*H*OH), 4.70 (m, 1 H, CHOCO–); mass spectrum m/e 354, 336, 292, 270, 252. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.37; H, 11.97.

17 prepared earlier was compared with a sample of 3(S)-hexyl-4(S)-hydroxy-6(S)-undecyltetrahydro-2*H*-pyran-2-one prepared from tetrahydrolipstatin according to procedure of Barbier and Schneider:[6] mp 105–105.5 °C (mixed mp 105 °C); $[\alpha]^{25}_D$ = −3.8° (*c* 0.5, $CHCl_3$). They were identical by NMR, MS, and IR.

(3*S*,4*S*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-hexyl-6-undecyltetrahydro-2*H*-pyran-2-one (20). To a solution of 500 mg (1.41 mmol) of **17** in 5 mL of dimethylformamide was added 0.92 mL (5.25 mmol) of *N*,*N*-diisopropylethylamine and 635 mg (4.23 mmol) of *tert*-butyldimethylsilyl chloride. The mixture was stirred for 48 h and then diluted with ice-cold water and extracted with ether. The organic solution was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed (20:1 hexanes/ETOAc) and gave 600 mg (90%) of **20**: $[\alpha]^{25}_D$ = +15.96° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1720, 838 cm^{-1}; ^1H NMR (400 MHz) δ 0.07 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.88 (m, 15 H), 1.20–1.40 (b, 26 H), 1.55 (b m, 2 H), 1.6–1.8 (m, 2 H), 1.9–2.1 (m, 2 H), 2.2 (m, 1 H), 4.22 (m, 1 H, SiCHO), 4.64 (m, 1 H, CHO(CO)); mass spectrum m/e 468, 411, 393, 383, 336, 313, 75. Anal. Calcd for $C_{28}H_{56}O_3Si$: C, 71.73; H, 12.04, Si, 5.99. Found: C, 72.04; H 12.08, Si, 5.93.

(2*S*,3*S*,5*S*)-Benzyl 2-Hexyl-3-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxyhexadecanoate (21). To a mixture of 980 mg (2.09 mmol) of **20** in 48 mL of dioxane was added 2.3 mL of 1 N potassium hydroxide. After 80 min, the reaction mixture was concentrated under vacuum. The residue was azeotroped twice with toluene and dissolved in a mixture of 10.5 mL of THF and 8.5 mL of hexamethylphosphorus triamide. To the resulting solution was added 1.25 mL (12.5 mmol) of benzyl bromide. After 16 h at room temperature, the mixture was diluted with hexane, washed with water and brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (30:1 hexanes/EtOAc) and gave 981 mg (81%) of **21**: $[\alpha]^{25}_D$ = −1.77° (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 1728, 698 cm^{-1}; ^1H NMR (400 MHz) δ 0.11 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.9 (m, 15 H), 1.28–1.37 (b m, 28 H), 1.40–1.68 (m, 4 H), 2.55 (d, 1 H, OH), 2.65 (b m, 1 H, CHCOO), 3.67 (b, 1 H, CHOSi), 4.18 (m, 1 H, CHO), 5.14 (AB, 2 H, $ArCH_2O$), 7.32 (m, 5 H, Ar); mass spectrum m/e 576, 561, 519, 501, 427, 411, 383. Anal. Calcd for $C_{35}H_{64}O_4Si$,: C, 72.86; H, 11.18; Si, 4.87, Found: C, 72.92; H, 11.14, Si, 4.64.

(2*S*,3*S*,5*S*)-Benzyl 2-Hexyl-3-[(*tert*-butyldimethylsilyl)oxy]-5-(benzyloxy)hexadecanoate (22). To a solution of 980 mg (1.70 mmol) of **21** in a mixture of 12 mL of dichloromethane and 24 mL of cyclohexane was added 0.70 mL (3.4 mmol) of benzyl trichloroacetimidate. The resulting mixture was cooled to 0 °C, and 50 μL of trifluoromethanesulfonic acid was added. After 5 h at room temperature, the mixture was cooled to 0 °C and filtered and the residue was washed with 1:2 dichloromethane/cyclohexane. The filtrate was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (20:1 hexanes/EtOAc) and gave 800 mg (71%) of **22**: $[\alpha]^{25}_D$ = +15.81° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 1728, 832, 695 cm^{-1}; ^1H NMR (400 MHz) δ 0.02 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.9 (m, 15 H, 2 × CH_3, $SiC(CH_3)_3$), 1.1–1.4 (b, 28 H, CH_2), 1.48 (m, 2 H), 1.6 (m, 1 H), 1.8 (m, 1 H), 2.60 (m, 1 H, CHCO), 3.55 (m, 1 H, CHO), 4.0 (m, 1 H, CHO), 4.45 (AB, 2 H, $ArCH_2O$), 5.1 (s, 2 H, $ArCH_2OCO$), 7.3 (m, 10 H, Ar); mass spectrum m/e 609, 518, 501, 393. Anal. Calcd for $C_{42}H_{70}O_4Si$,: C, 75.62; H, 10.58. Found: C, 75.77; H, 10.55.

(2*S*,3*S*,5*S*)-Benzyl 2-Hexyl-3-hydroxy-5-(benzyloxy)hexadecanoate (23). To a solution of 100 mg (0.15 mmol) of **22** in a mixture of 1.8 mL of acetonitrile and 0.9 mL of THF at 0 °C was added 0.7 mL of 48% aqueous hydrofluoric acid. The mixture

was stirred for 2 h and then diluted with ether, washed with water, saturated sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (5:1 hexanes/EtOAc) and gave 78 mg (94%) of **23**: $[\alpha]^{25}_D$ = +19.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1722, 697 cm^{-1}; ^1H NMR (400 MHz) δ 0.85 (m, 6 H, 2 × CH_3), 1.18–1.32 (b m, 28 H), 1.53 (m, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 2.48 (m, 1 H, CHO), 3.65 (m, 2 H, CHO and OH), 3.92 (m, 1 H, CHO), 4.41 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2O$), 4.58 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2O$), 5.15 (m, 2 H, $ArCH_2OCO$), 7.3 (m, 10 H, Ar); mass spectrum *m/e* 553, 445, 427, 337, 319, 301. Anal. Calcd for $C_{36}H_{56}O_4$: C, 78.2; H, 10.21. Found: C, 78.01; H, 10.21.

(2*S*,3*S*,5*S*)-2-Hexyl-3-hydroxy-5-(benzyloxy)hexadecanoic Acid (24). To a solution of 475 mg (0.86 mmol) of **23** in 9 mL of ethanol was added 2.6 mL of 1 N sodium hydroxide. The reaction mixture was heated at 50 °C for 4 h, cooled, and then concentrated. The residue was diluted with water, acidified with 1 N hydrochloride acid, and extracted with ethyl acetate. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed (1:1 hexanes/EtOAc, 9:1 chloroform/methanol) and gave 392 mg (99%) of **24**: $[\alpha]^{25}_D$ = +12.06° (*c* 0.92, $CHCl_3$); IR ($CHCl_3$) 1747, 1572, 698 cm^{-1}; ^1H NMR (400 MHz) δ 0.87 (m, 6 H, 2 × CH_3), 1.1–1.39 (b, 32 H, CH_2's), 1.5–1.7 (b d, 2 H), 2.3 (b s, 1 H, CHCO), 3.7 (b s, 1 H, CHO), 3.9 (b s, 1 H, CHO), 4.5 (b d, 2 H, $ArCH_2$), 7.28 (s, 5 H, Ar); mass spectrum *m/e* 462, 444, 307, 144.

(2′*S*,3*S*,4*S*)-3-Hexyl-4-[2′-(benzyloxy)tridecyl]oxetan-2-one (25). To a solution of 363 mg (0.78 mmol) of **24** in 10 mL of dry pyridine at 0 °C was added 0.19 mL (1.6 mmol) of benzenesulfonyl chloride. After 17 h at 0 °C, the mixture was added to 20 mL of cold brine. This was extracted with ether, dried ($MgSO_4$), and concentrated. The residue was chromatographed (10:1 hexanes/EtOAc) and gave 239 mg (69%) of **25**: $[\alpha]^{25}_D$ = −3.44° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 1818, 698 cm^{-1}; ^1H NMR (400 MHz) δ 0.84 (m, 6 H), 1.2–1.5 (b, 27 H), 1.6 (m, 1 H), 1.65 (m, 2 H), 1.75 (m, 1 H), 1.92 (m, 1 H), 2.15 (m, 1 H), 3.25 (m, 1 H, CHCO), 3.52 (m, 1 H, CHO), 4.43 (m, 1 H, CHOCO), 4.44 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2$), 4.54 (AB, J_{gem} = 12 Hz, 1 H, $ArCH_2$), 7.32 (m, 5 H, Ar); mass spectrum *m/e* 444, 416, 398, 338, 291. Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.61; H, 10.80.

(2′*S*,3*S*,4*S*)-3-Hexyl-4-(2′-hydroxytridecyl)oxetan-2-one (7). To a solution of 224 mg (0.505 mmol) of **25** in 7 mL of THF was added 40 mg of 10% Pd/C. The mixture was stirred under 1 atm of hydrogen. After 3 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was crystallized from hexane and gave 170 mg (95%) of **7**: mp 63–64 °C (hexanes); $[\alpha]^{25}_D$ = −16.3° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3545, 1812 cm^{-1}; ^1H NMR (400 MHz) δ 0.9 (m, 6 H, 2 × CH_3), 1.2–1.38 (b, 26 H, CH_2), 1.43 (m, 1 H), 1.5 (m, 1 H), 1.61 (d, 1 H), 1.7–1.91 (m, 3 H), 2.0 (m, 1 H), 3.32 (m, 1 H, CHCO), 3.8 (s, 1 H, CHO), 4.42 (m, 1 H, CHOCO); mass spectrum *m/e* 354, 336, 292, 270, 252, 199, 181. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.73; H, 12.11.

(1*S*,2′*S*,3′*S*)-*N*-[(Phenylmethoxy)carbonyl]-L-leucine 1-[(3′-Hexyl-4′-oxo-2′-oxetanyl)methyl]dodecyl Ester (26). To a solution of 590 mg (2.22 mmol) of (*S*)-*N*-[(benzyloxy)carbonyl]leucine in 6 mL of dichloromethane at 4 °C was added 228 mg (1.11 mmol) of 1,3-dicyclohexylcarbodiimide. After 15 min, the precipitate was removed by vacuum filtration. The filtrate was concentrated, dissolved in 4.5 mL of dimethylformamide, and then added to a solution of 197 mg (0.55 mmol) of 7 and 8 mg of 4-(*N*,*N*-dimethylamino)pyridine in 2.5 mL of dimethylformamide. After 35 min the reaction mixture was diluted with 15 mL of cold water and extracted with ether. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (6:1 hexanes/EtOAc) and crystallized from pentane and gave 283 mg (85%) of **26**: mp 47.5–48.5 °C, $[\alpha]^{25}_D$ = −23.86° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3335, 1842, 1730, 1692, 697 cm^{-1}; ^1H NMR (400 MHz) δ 0.85 (t, 6 H), 0.95 (t, 6 H), 1.2 (b, 27 H), 1.6 (m, 3 H), 1.7 (m, 3 H), 1.96 (m, 1 H), 2.15 (m, 1 H), 3.2 (m, 1 H, CH), 4.25 (m, 1 H, CHO), 4.35 (m, 1 H, CHO), 5.0 (b s, 1 H, OH), 5.08 (d, 1 H, NH), 5.11 (b s, 2 H, $ArCH_2$), 7.32 (s, 5 H); mass spectrum *m/e* 601, 557, 466, 449, 382, 337. Anal. Calcd for $C_{36}H_{59}NO_6$: C, 71.84; H, 9.88; N, 2.33. Found: C, 71.92; H 9.97; N 2.36.

Tetrahydrolipstatin (4). To a solution of 230 mg (0.382 mmol) of **26** in 6 mL of THF was added 28 mg of 10% Pd/C. The mixture was stirred under 1 atm of hydrogen. After 4 h, the catalyst was removed by filtration and the filtrate was concentrated. The residue was treated with 0.36 mL (0.47 mmol) of formic acetic anhydride. After 5 min, the mixture was diluted with ether. The organic solution was washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. The residue was crystallized from pentane to provide 137 mg (72%) of **4**: mp 42–43 °C (pentane); $[\alpha]^{25}_D$ −34.58° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3340, 1840, 1722, 1710, 1680, 1668 cm^{-1}; ^1H NMR (400 MHz) δ 0.9 (m, 6 H), 1.0 (m, 6 H), 1.2–1.5 (b, 28 H), 1.52–1.9 (m, 5 H), 2.0 (m, 1 H), 2.15 (m, 1 H), 3.22 (m, 1 H), 4.3 (m, 1 H), 4.7 (m, 1 H), 5.12 (m, 1 H), 5.9 (d, 1 H), 8.22 (d, 1 H); mass spectrum *m/e* 495, 480, 292, 57, 29. Anal. Calcd for $C_{29}H_{53}NO_5$: C, 70.26; H, 10.78; N, 2.83. Found: C, 70.05; H, 10.81; N, 2.78.

Acknowledgment. We express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche, Inc., for determination of spectral and analytical data.

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 18. Reductions with Hydrides

Genevieve D. Paderes, Pascal Metivier,† and William L. Jorgensen*

Department of Chemistry, Yale University, New Haven, Connecticut 06511

Received January 14, 1991 (Revised Manuscript Received April 17, 1991)

A reaction module for processing the reduction chemistry of metal hydrides and boranes has been developed for the computer program CAMEO. The general algorithm analyzes and classifies reductive transformations in terms of fundamental mechanistic steps. Central to this algorithm has been the development of general functional group reactivity tables from which competitions between viable reducible sites are assessed. Existing routines for calculating FMO energies, bond dissociation energies, ion stabilities, pK_a's, and Taft E_s parameters have been utilized for the determination of chemo- and regioselectivities. Examples of reaction sequences demonstrating the current predictive capabilities of CAMEO are presented.

I. Introduction

CAMEO, an interactive computer program designed to predict the outcome of organic reactions given the reactants and conditions, is under continuous expansion.[1] Recently, the scope of the program has been enhanced to

† Present address: Rhone-Poulenc Recherches, 69192 Saint-Fons, France.

(1) For a review, see: Jorgensen, W. L.; Laird, E. R.; Gushurst, A. J.; Fleischer, J. M.; Gothe, S. A.; Helson, H. E.; Paderes, G. D.; Sinclair, S. *Pure Appl. Chem.* **1990**, *62*, 1921.

0022-3263/91/1956-4718$02.50/0