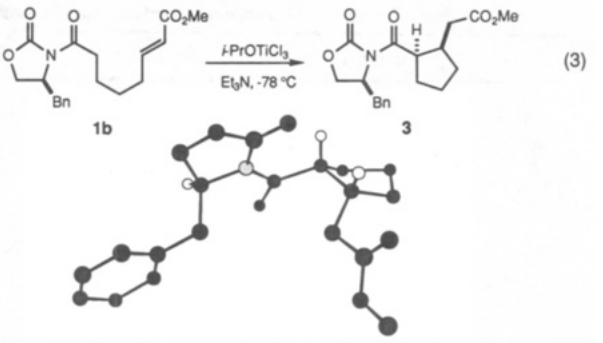
carboxylic acid derivative with unsaturated ketones.

The reactions of the *N*-propionyloxazolidone **1a** with methyl acrylate and acrylonitrile were also found to be highly diastereoselective (entries B–D).[12] Reaction optimization with these Michael acceptors leads to a slight modification of the preceding conditions with the adoption of *i*-PrOTiCl$_3$ as the enolizing Lewis acid, which, in concert with DIPEA[13] (0 °C, 1 h), is also known to quantitatively transform these substrates into their derived alkoxytitanium enolates.[1] In contrast to the reactions of these enolates with unsaturated ketones (entries A and E), acrylate and acrylonitrile electrophiles react at convenient temperatures (0–25 °C) without the necessity of utilizing a second equivalent of Lewis acid. Under these conditions, acid-labile *tert*-butyl esters survive intact (entry D).[14] These conjugate additions were also shown to be applicable to the other substrates shown in entries F and G. In both cases the reactions with acrylonitrile proceeded in good yield with the formation of only one detectable product diastereomer.

The scope of these reactions does not extend to include β-substituted, α,β-unsaturated esters or nitriles, which are unreactive, even as their Lewis acid conjugates; however, this restriction does not apply to α,β-unsaturated ketones. Unfortunately, this latter family of Michael acceptors shows no appreciable stereocontrol with regard to the additional prochiral center resident on the electrophilic olefin (entry E).

The application of this methodology to intramolecular reactions was also evaluated (eq 3). The reaction of substrate **1b** proved to proceed well when *i*-PrOTiCl$_3$ was employed as the enolizing Lewis acid. In contrast to the intermolecular cases, reaction diastereoselection was markedly better when triethylamine rather than DIPEA was used as the enolizing base. The optimized conditions involve addition of the substrate to a mixture of *i*-PrOTiCl$_3$ (2.0 equiv) and triethylamine (1.0 equiv) in CH_2Cl_2 (–78



(3)

°C, 5 h). Under these conditions, **1b** affords a 93:7 ratio of diastereomers from which the major adduct **3** (88%) was isolated as a crystalline solid, mp 136.6–137 °C, after chromatographic purification. The X-ray structure of **3** is fully consistent with the expected sense of asymmetric induction on the chelated *Z* enolate while the cis ring stereochemistry implicates the requirement for internal metal relocation during the Michael process.

We have also examined the Michael reactions of the Oppolzer *N*-propionylsultam[15] (entry H). The reaction with ethyl vinyl ketone proceeded with high stereoselectivity but in modest yield (33%), the principal side reaction being competing 1,2 addition (54%). These results are surprising in light of the analogous reaction with *N*-propionyloxazolidone **1a**, which affords no 1,2-addition products. Reaction of the sultam with either methyl acrylate or acrylonitrile could not be induced under a variety of conditions. The full scope of these and related reactions will be reported in due course.

Acknowledgment. Support has been provided by the NIH, the NSF, and Merck. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities. A postdoctoral fellowship for T.C.S. (NIH) is gratefully acknowledged.

Supplementary Material Available: Experimental procedures and spectral data for all new compounds (10 pages). Ordering information is given on any current masthead page.

(12) The sense of asymmetric induction in these reactions has been assigned by analogy.

(13) As a point of mechanistic interest, all of the bimolecular reactions employing DIPEA proceed with markedly better stereoselectivity than the analogous reactions using triethylamine as the enolizing base.

(14) This transformation was carried out by James R. Gage of this laboratory.

(15) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772.

Enantioselective Synthesis of β-Hydroxy δ-Lactones: A New Approach to the Synthetic Congeners of 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors

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Summary: Chiral β,δ-diketo esters derived from Taber's chiral alcohol or its enantiomer were reduced either in one step (Et_2BOMe, $NaBH_4$, THF–MeOH) or in two steps (2 equiv $HAl(i\text{-}Bu)_2$, THF; Et_2BOMe, $NaBH_4$, THF–MeOH) to give *syn*-β,δ-dihydroxy esters with high diastereoselectivity. Hydrolysis of the esters followed by lactonization afforded the title lactones of high optical purity ranging from 49 to >97% ee.

The discovery of compactin (**1a**) and mevinolin (**1b**), highly potent inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG Co-A) reductase,[1] led to a number of publications concerning the synthesis and biological properties of their structural analogues (e.g., **2**), all of which

(1) Endo, A. *J. Med. Chem.* **1985**, *28*, 401.

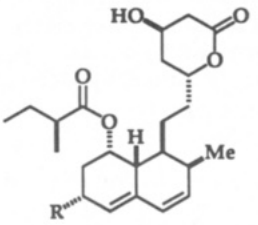
0022-3263/91/1956-5752$02.50/0

Table I. One-Pot Reduction[a] of 3 or 3′ To Give Lactone 5 or 5′

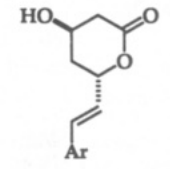
entry	diketo ester	borane chelating agent	dihydroxy ester (% yield)	lactone (% yield)	trans:cis	config	% ee
1	**3a**	Et_2BOMe	**4a** (85)	**5a** (76)	>95:5	3*S*,5*R*	49[b]
2	**3a**	Et_2BOMe[c]	**4a** (78)	**5a** (50)	95:5	3*S*,5*R*	37[b]
3	**3a**	MeO-9-BBN	**4a** (31)	**5a** (66)	97:3		~0
4	**3a**	Me_2BBr	**4a** (35)	**5a** (61)	70:30	3*R*,5*S*	58[b]
5	**3b**	Et_2BOMe	**4b** (83)	**5b** (63)	82:18	3*S*,5*R*	66[d]
6	**3′b**	Et_2BOMe	**4′b** (79)	**5′b** (65)	79:21	3*R*,5*S*	64[d]

[a] The reduction was carried out in THF–MeOH at −78 °C and at rt overnight using the borane chelating agent (1.1 equiv) and $NaBH_4$ (3–5.6 equiv). [b] Determined by HPLC using CHIRALCEL OA column (Daicel). [c] This run was effected using 2.1 equiv of Et_2BOMe. [d] Determined by HPLC using CHIRALCEL AD column (Daicel).

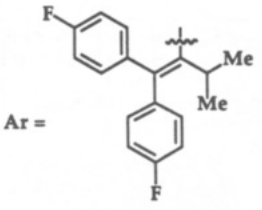
contain a *trans*-β-hydroxy δ-lactone.[2,3] The most commonly used synthetic method involves chelation-controlled reduction of chiral aldols to *syn*-1,3-diols, which then are converted into the hydroxy lactones.[3] An alternative approach is a one-step reduction of β,δ-diketo esters to β,δ-dihydroxy esters,[4] but this was successful only with respect to diastereoselectivity; no method for enantioselective reduction was available at that time. We report herein methodology for the asymmetric synthesis of the title compounds by this direct approach.



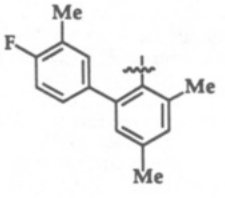
1a: R = H, compactin
1b: R = Me, mevinolin



2a (Ar = a)
2b (Ar = b)



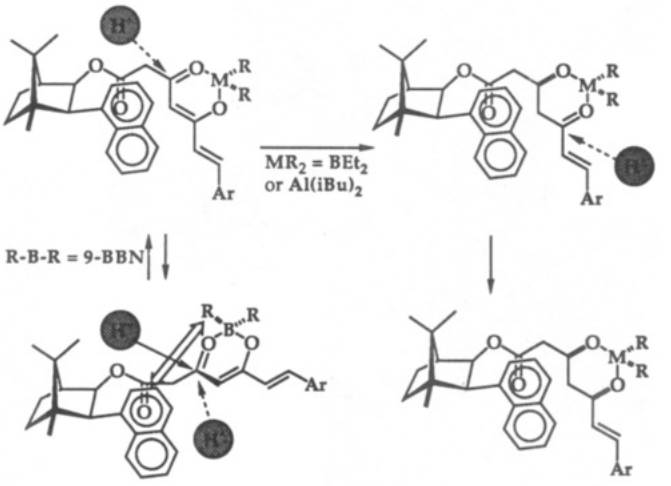
a



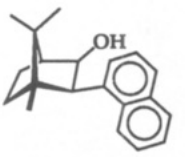
b

Previous research in our laboratory showed that discrimination between the *re* and *si* face of the two carbonyls in β,δ-diketo esters by a chiral reagent is extremely difficult, and thus it was considered essential to create a dissymmetric environment around the diketo ester by reducing the conformational freedom of the molecule and blocking one face of the diketo ester moiety. To fulfill

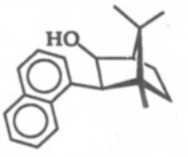
Scheme I. Stereochemical Course of the Reduction of 3



these criteria, we have chosen β,δ-diketo esters **3**[5] derived from Taber's chiral alcohol *T*-OH or its enantiomer HO-*T*′.



T-OH



HO-*T*′

The naphthalene ring of **3** should act as a steric shield,[6b] and an additional interaction like chelation would freeze the free rotation of the diketo ester to direct the hydride attack from the *re* face to give dihydroxy esters **4**. This plan worked out well after studying the reduction in THF–MeOH mixture in the presence of a variety of chelating agents. The reduction with sodium borohydride in the presence of Et_2BOMe proved to be a good choice for this reaction. Both diastereoselectivity and enantioselectivity[7] of the reduction were moderately high as estimated on the hydroxy lactones **5** and **5′** (entries 1, 2, 5, and 6 in Table I). Starting from **3′b**, we could achieve the synthesis

(2) Review: (a) Rosen, T.; Heathcock, C. *Tetrahedron* **1986**, *42*, 4909. Recent publications: (b) Wess, G.; Kesselar, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstien, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545. (c) Boquel, P.; Chapleur, Y. *Ibid.* **1990**, *31*, 1869. (d) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Ibid.* **1990**, *31*, 3619. (e) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; Da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018 and references cited therein.

(3) Recent references: (a) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 21. (b) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *Ibid.* **1990**, *33*, 31. (c) Beck, G.; Kessellar, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; Vonkerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *Ibid.* **1990**, *33*, 52. (d) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Vonkerekjarto, B.; Kesseller, K.; Krause, R.; Schubert, W.; Wess, G. *Ibid.* **1990**, *33*, 61. (e) Prasad, K.; Chen, K. M.; Repic, O.; Hardtmann, G. E. *Tetrahedron Asymmetry* **1990**, *1*, 307 and references cited therein.

(4) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467.

(5) Diketo esters **3** or **3′** were prepared by acylation of the acetoacetate of Taber's alcohol *T*-OH or its enantiomer HO-*T*′ with amides ArCH=CHCON(Me)OMe in moderate to good yields.[4] The δ-keto groups of **3** are found to exist in an enol form. The acetoacetates were in turn prepared by transesterification between methyl acetoacetate and *T*-OH (or HO-*T*′).[6]

(6) (a) Taber, D. F.; Raman, T.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. (b) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488. (c) Taber, D. F.; Amedio, J. C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

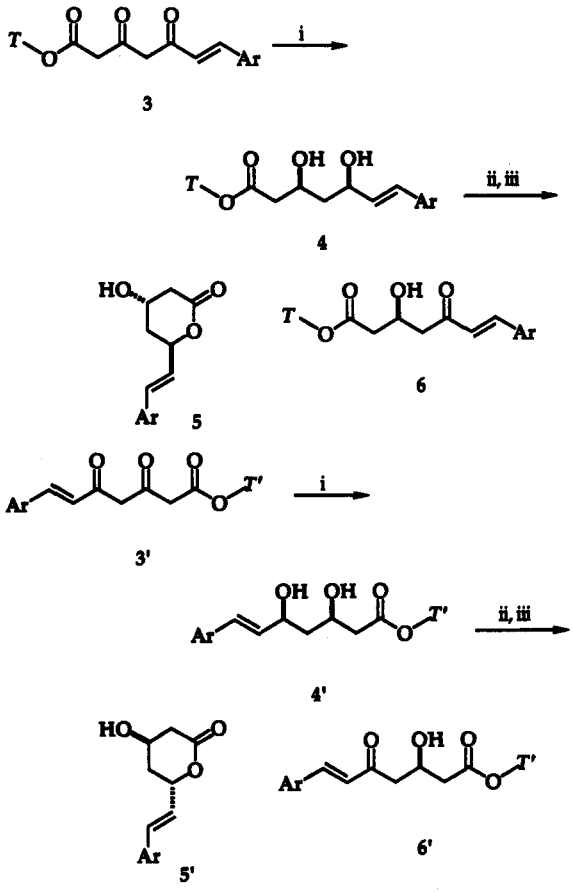
(7) The diastereoselectivity and the enantioselectivity were estimated using a chiral HPLC column (see footnotes of Table I) after converting **4** into **5**.

Table II. Two-Step Reduction of 3 or 3′ and Synthesis of Lactone 5 or 5′[a]

entry	diketo ester	hydroxy keto ester (% yield)	isomer ratio	dihydroxy ester (% yield)	lactone (% yield)	trans:cis[c]	config	% ee[c]
1	3a	6a (85)	>95:5	4a (80)[b]	5a (53)	100:0	3S,5R	>95
2	3′a	6′a (70)	>95:5	4′a (78)[b]	5′a (56)	99:1	3R,5S	>97
3	3c	6c (78)	>95:5	4c (81)[b]	5c (60)	100:0	3S,5R	>92

[a] The reduction of 3 or 3′ was effected in THF using DIBAL (2 equiv) at −78 °C to give 6 or 6′, respectively. [b] The reduction was carried out under the conditions shown in Table I. [c] Determined by HPLC using CHIRALCEL OA column (Daicel).

of lactone 5′b,[8] which is a potent HMG-CoA reductase inhibitor (entry 6).



a: Ar = Ph; b: Ar = a; c: Ar = 4-Me-C_6H_4-

i: $NaBH_4$, Et_2BOMe, THF-MeOH, -78 °C to rt;

ii: NaOH aq; iii: PhMe, Δ

The selectivity of the reduction deserves comment. The stereochemical outcome of the asymmetric induction observed using Et_2BOMe–$NaBH_4$ is consistent with the transition state shown in Scheme I. The boron chelating agent interacts with the β,δ-diketo moiety, thereby leaving the ester carbonyl free and allowing the hydride to attack the β-carbonyl from the face opposite to the naphthyl ring. This corresponds to the enantioselectivity observed by Taber in β-keto ester reductions that were assumed to proceed through an anti conformation.[6b] The absence of asymmetric induction using MeO-9-BBN (entry 3) may be attributed to steric repulsion between 9-BBN and the naphthalene ring and/or *gem*-dimethyls of the chiral alcohol, thus forcing the β,δ-diketo ester away from the face-blocking naphthalene ring and thereby giving equal opportunity for the hydride to attack from both sides of the β-carbonyl group. Accordingly, the reduction, although diastereoselective, was not enantioselective.[9] To our surprise, use of Me_2BBr as the chelating agent resulted in moderate diastereoselectivity but opposite asymmetric induction (entry 4).[10]

Although we have established a one-pot procedure for 1,3-diastereoselective reduction, there is still a scope for improving the stereoselectivity. The following two-step method was found to be very efficient: reduction of 3 (or 3′) with 2 equiv of diisobutylaluminum hydride (DIBAL)[11] to give β-hydroxy-δ-keto esters 6 (or 6′) and further reduction with $NaBH_4$ in the presence of Et_2BOMe (Table II). The diastereoselectivity exceeded 99:1, and the enantiomer excess ranged from 92 to 97%. The chemical yields of the each step also were satisfactory.[12]

In conclusion, stereoselective reduction of β,δ-diketo esters derived from the Taber's chiral alcohol *T*-OH or its enantiomer HO-*T*′ through a one-step or two-step procedure provides chiral β,δ-dihydroxy esters or lactones, some of which are expected to be highly potent hypocholesterolemic agents. Synthetic applications of this methodology are in progress in our laboratories.

Supplementary Material Available: Typical procedures for the preparation of diketo esters, the one-step reduction, and the two-step reduction, as well as characterization data for the compounds (7 pages). Ordering information is given on any current masthead page.

(8) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jandralla, H.; Kesselar, K.; Wess, G.; Schubert, W.; Granzer, E.; Kerekjarto, B. V.; Krause, R. *Tetrahedron Lett.* **1988**, *29*, 929.

(9) Reduction of 3 with $Zn(BH_4)_2$–$ZnCl_2$, which was assumed by Taber and his co-workers[6b] to proceed through syn conformation, gave similar results to entry 3 of Table I.

(10) Probably the less bulky Me_2B group could interact also with the ester carbonyl to induce a syn conformation,[6b] which was responsible for the 3*R* configuration of 5b.

(11) Chelation-controlled reduction of β-hydroxy ketones with DIBAL, see: Kiyooka, S. I.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.

(12) The experimental procedure for 5c is typical (entry 3, Table II). To a THF (1.5 mL) solution of diketo ester 3c (173 mg, 0.34 mmol) at −78 °C under Ar was added DIBAL (1.02 M toluene solution, 0.70 mL, 0.72 mmol), and the mixture was stirred for 4 h. The reaction mixture was quenched with 1 M HCl (1 mL) and diluted with ethyl acetate (20 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were washed with 5% $NaHCO_3$ (20 mL) and saturated NaCl(aq) solution and dried over $MgSO_4$. Concentration in vacuo followed by preparative TLC (silica gel, 20% ethyl acetate in hexane) gave 6c (135 mg, 78% yield), $[\alpha]_D^{20}$ −108.90° (*c* 1.50, $CHCl_3$). The diastereomeric ratio was found to be >95:5 (HPLC, Si 60, hexane–ethanol (80:1)). β-Hydroxy δ-keto ester 6c (49 mg, 0.10 mmol) was dissolved in THF (1 mL)–MeOH (0.2 mL), and Et_2BOMe (13 μL, 9.6 mg, 0.10 mmol) was added at −78 °C under Ar. The reaction mixture was stirred at rt for 15 min and cooled again to −78 °C. $NaBH_4$ (8 mg, 0.21 mmol) was added, and the reaction mixture was stirred at −78 °C for 4 h and at rt overnight. Workup and preparative TLC (silica gel, 30% EtOAc in hexane) afforded pure dihydroxy ester 4c (40 mg, 81% yield), $[\alpha]_D^{20}$ −87.00° (*c* 3.00, $CHCl_3$). This (30 mg, 0.06 mmol) was hydrolyzed with aqueous 1 M NaOH (0.15 mL, 0.15 mmol) in MeOH (2 mL) for 45 h at rt. Acidic extraction gave a crude acid, which was heated in dry toluene (3 mL) at 110 °C for 5 h. Concentration followed by preparative TLC (CH_2Cl_2–acetone (4:1)) afforded pure lactone 5c (8.2 mg, 60% yield), mp 126–127 °C, $[\alpha]_D^{20}$ −5.69 (*c* 0.65, $CHCl_3$), 92% ee (HPLC, CHIRALCEL OA, hexane–2-propanol (9:1)). Recovery of *T*-OH was more than 90% in all hydrolysis and lactonization reactions. Similarly, 5a was obtained whose absolute configuration was determined by converting 4a through hydrogenation, hydrolysis, and lactonization into the dihydro derivative of 5a. The sign of its optical rotation $[\alpha]_D^{20}$ −60.8 (*c* 1.23, $CHCl_3$) is opposite to that reported for (*R*,*R*)-β-hydroxy lactone, $[\alpha]_D^{24}$ +48.8 (*c* 0.20, $CHCl_3$).[13] The low $[\alpha]_D$ value reported by Clive et al. should be attributed to partial racemization in their process.

(13) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101.