Tetrahedron Letters, Vol. 34, No. 3, pp. 513-516, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

STEREOSELECTIVE REDUCTION OF β,δ-DIKETO ESTERS DERIVED FROM TARTARIC ACID. A FACILE ROUTE TO OPTICALLY ACTIVE 6-OXO-3,5-*syn*-ISOPROPYLIDENEDIOXYHEXANOATE, A VERSATILE SYNTHETIC INTERMEDIATE OF ARTIFICIAL HMG Co-A REDUCTASE INHIBITORS.

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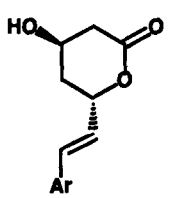
Abstract: Reduction of β,δ-diketo esters derived from tartaric acid with $HAl(i\text{-}Bu)_2$ gave stereoselectively β-hydroxy-δ-keto esters which were reduced with $NaBH_4$ and Et_2BOMe to β,δ-*syn*-dihydroxy esters. This strategy was successfully applied to the synthesis of *t*-butyl (3*R*,5*S*)-6-oxo-3,5-isopropylidenedioxyhexanoate starting from D-tartrate.

In view of increasing number of publications on artificial HMG Co-A reductase inhibitors having a common structure **1**,[1] straightforward synthetic methods of these targets have been awaited. We have shown[2] that *t*-butyl 6-oxo-3,5-*syn*-isopropylidenedioxyhexanoate (**2**) is a versatile synthetic intermediate of highly potent artificial HMG Co-A reductase inhibitor NK-104 (**1a**).[3] Therein, we obtained the requisite aldehyde **2** through oxidative cleavage of (*E*)-7-phenyl-3,5-*syn*-isopropylidenedioxy-6-heptenoate of the Taber's alcohol.[4,5] We have since been studying alternative methods and report herein a new one which is based on stereoselective two-step reduction of a β,δ-diketo ester derived from tartaric acid.



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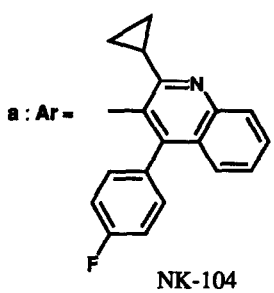
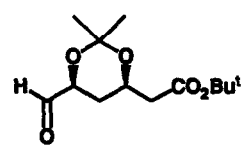


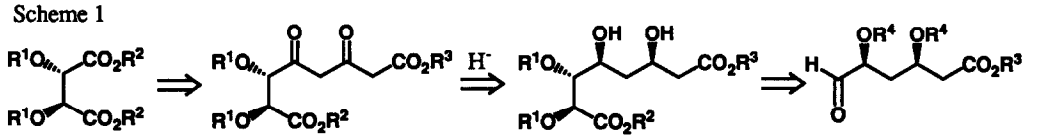
NK-104



2

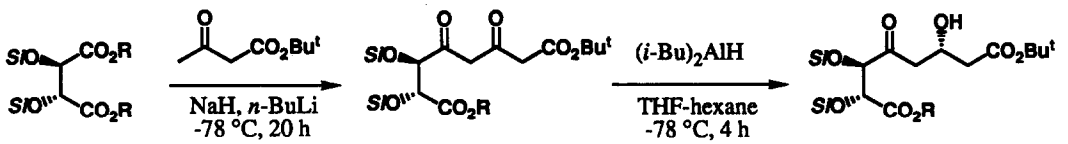
Our synthetic strategy is summarized in Scheme 1. Properly protected tartrate **I** is converted into a β,δ-diketo ester **II**. Reduction of **II** would undergo stereoselectively to give a β,δ-dihydroxy ester **III**. When a bulky protecting group was employed for R^1, conformation of **II** will be fixed,[6] thus allowing hydride to attack *si* face of the β-carbonyl. Protection and deprotection of the diol moieties of the resulting **III**, followed by oxidative glycol cleavage, should give the desired aldehyde **IV**.

Scheme 1



I II III IV

Tartrate **3**, doubly protected by *t*-butyldimethylsilyl group, was allowed to react with a dianion of *t*-butyl acetoacetate to give β,δ-diketo ester **4** in good yield. Even if we employed excess amount of the dianion, we could isolate **4** only. Methyl ester **4a** was allowed to react with 2 eq of diisobutylaluminium hydride (DIBAL) in THF-hexane (1 : 1) at -78°C to afford β-hydroxy-δ-keto ester **5a** and its diastereomer in a ratio of 89 : 11[7] in 51% yield. In cases of ethyl ester (**4b**) and isopropyl ester (**4c**), diastereoselectivity and chemical yield increased to 97 : 3, 56% and 99 : 1, 61% respectively. The stereochemical assignment was made by transformation (*cf.* Scheme 2) of **5a** to *t*-butyl 6-hydroxy-3,5-isopropylidenedioxyhexanoate (*cf.* compound **iii** in footnote 12) and comparison of its optical rotation.



3
Si = *t*-$BuMe_2Si$

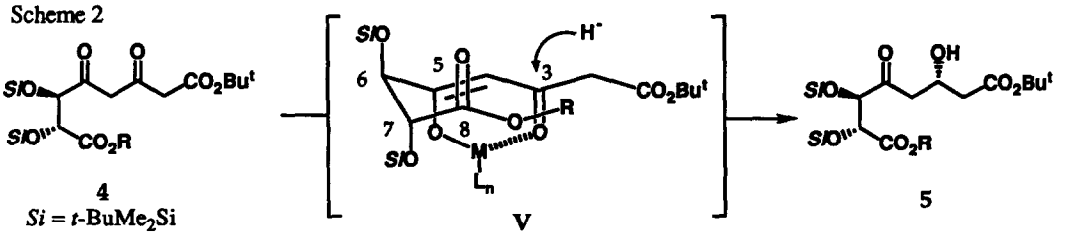
4

5

	R	yield of **4** (%)	yield of **5** (%)	diastereoselectivity of **5**
a	Me	76	51	89 : 11
b	Et	74	56	97 : 3
c	*i*-Pr	74	61	99 : 1

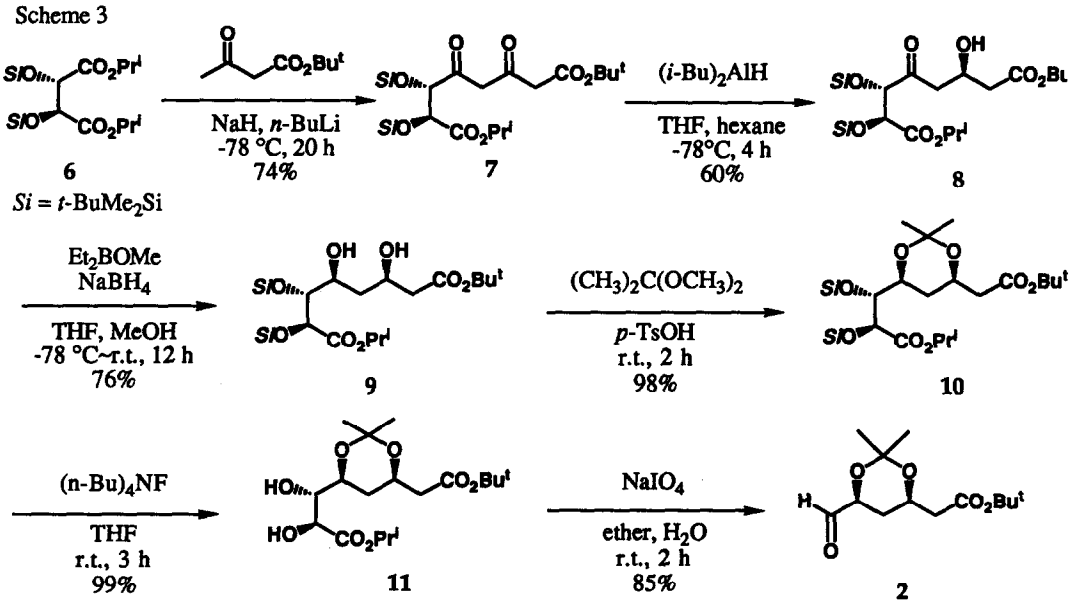
The stereochemical outcome of asymmetric induction observed using DIBAL is consistently understood by the transition state illustrated in Scheme 2.[8] The C(5)-carbonyl of **4** is enolized as evidenced by ^{1}H-NMR, and thus 1 eq of DIBAL is consumed to give a chelate like **V**. The conformation **V** is assumed to be fixed by the silyl-protected glycol part so that these bulky silyloxy group is positioned *anti* due to steric repulsions. In addition, dipole repulsion between 3- and 8-oxo groups is expected to be operating to give **V** predominantly. Thus, hydride attacks C(3)-carbonyl preferentially from *si*-face, opposite to ester part at C(8). This model explains well the fact that the diastereoselectivity is improved by a bulky R, *i.e.* isopropyl group.[9]

Scheme 2



To give access to final aldehyde **2** having correct absolute configuration, we started with β,δ-diketo ester **7** which was prepared by the reaction of silyl-protected diisopropyl D-tartrate **6** with the dianion of *t*-butyl acetoacetate (Scheme 3). Reduction of **7** with DIBAL afforded β-hydroxy-δ-keto ester **8** in 60% yield. This was reduced by sodium borohydride in the presence of Et_2BOMe to give exclusively *syn*-β,δ-dihydroxy ester **9** in 76% yield. After the protection of the resulting 1,3-diol part by acetonide, *t*-butyldimethylsilyl group was removed by treatment of tetrabutylammonium fluoride to afford 1,2-diol **11** in 98% yield. Oxidative cleavage of **11** with sodium metaperiodate in a mixture of ether and water gave the desired aldehyde **2**[11,12] in 85% yield.

Scheme 3



Stereoselective two-step reduction of a β,δ-diketo ester derived from D-tartaric acid provides a chiral β,δ-dihydroxy ester which was led in short steps to *t*-butyl (3*R*,5*S*)-6-oxo-3,5-isopropylidenedioxyhexanoate (**2**), a versatile intermediate for the synthesis of artificial HMG Co-A reductase inhibitors. Aldehyde **2** is easily transformed to various types of HMG Co-A reductase inhibitors through the Wittig-type olefination with the carbanion of $ArCH_2P(O)Ph_2$.[12]

References and Notes

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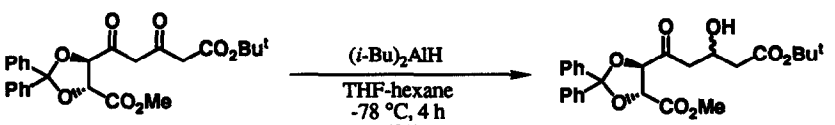
7 The ratio was determined by 400 MHz ^{1}H-NMR analysis.

8 This model corresponds well to the diastereoselectivity observed by Saito et al. in β-keto ester reductions. See ref 6 and also Saito, S.; Harunari, T.; Shimamura, N.; Asahara, M.; Moriwake, T. *Synlett* **1992**, 325.

9 Reduction of cyclic acetal **i** with DIBAL gave a 3 : 2 diastereomeric mixture of **ii**.

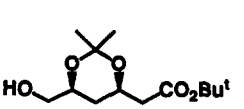


i ii

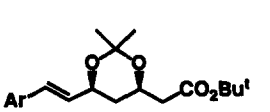
10 Aldehyde **2** showed $[\alpha]_D^{20}$ -27.1° (c 1.75, $CHCl_3$); IR ($CHCl_3$): 2950, 1735, 1435, 1380, 1080, 1030, 775, 730 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.40-1.48 (m, 1H), 1.45 (s, 9H), 1.45 (s, 3H), 1.49 (s, 3H), 1.83 (dt, J = 12.9, 2.8 Hz, 1H), 2.35 (dd, J = 15.4, 5.9 Hz, 1H), 2.46 (dd, J = 15.4, 7.1 Hz, 1H), 4.29-4.37 (m, 2H), 9.58 (d, J = 0.5 Hz, 1H); MS *m/z* 201 (M^+-Me, 24), 129 (31), 97 (36), 59 (100).

11 Since **2** is not stable, this was reduced ($NaBH_4$, MeOH, 0°C) to **iii**. Its optical rotation $[\alpha]_D^{20}$ -7.57 °(c 2.00, MeOH) was compared with authentic data [lit. $[\alpha]_D^{20}$ -3.7° (c 14.9, MeOH) (JP 01-1999454) and $[\alpha]_D^{20}$ -5.90° (c 2.0, MeOH) (JP 02-262537)] of (3*R*,5*S*) isomer.

12 Reaction of **2** (THF, r.t., 3 h) with Li[$ArCHP(O)Ph_2$], derived from $ArCH_2P(O)Ph_2$ (Ar = **a**) and lithium 2,2,6,6-tetramethylpiperazide, afforded an olefin **iv** (Ar = **a**, *E* : *Z* = 97 : 3) in 67% yield. This is successfully transformed to NK-104 (**1a**) in 74% yield by treatment with trifluoroacetic acid (*cf.* ref 2a). We thank Nissan Chemical Co. for supporting this research financially and providing information on NK-104. The olefin **iv** exhibited $[\alpha]_D^{20}$ +13.2° (c 1.25, $CHCl_3$); IR ($CHCl_3$): 3000, 1720, 1605, 1510, 1490, 1380, 1230, 1165, 1090, 1025, 840 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.04 (dd, J = 8.1, 3.3 Hz, 2H), 1.31-1.25 (m, 2H), 1.37 (s, 3H), 1.40-1.35 (m, 4H), 1.46 (s, 12H), 2.35 (dd, J = 15.6, 6.4 Hz, 1H), 2.43 (m, 1H), 2.54 (dd, J = 15.6, 6.7 Hz, 1H), 4.32-4.25 (m, 1H), 4.38-4.33 (m, 1H), 5.57 (dd, J = 16.3, 6.1 Hz, 1H), 6.55 (dd, J = 16.3, 1.2 Hz, 1H), 7.37-7.15 (m, 6H), 7.58 (dd, J = 6.6, 1.6 Hz, 1H), 7.95 (d, J =8.4 Hz, 1H); MS *m/z* 517 (M^+, 6), 461 (3), 448 (8), 402 (12), 386 (22), 290 (52), 288 (56), 275 (50), 57 (100).



iii



iv

(Received in Japan 1 October 1992)