ORGANIC LETTERS

2004
Vol. 6, No. 24
4439−4442

Asymmetric Synthesis of Deoxypolypropionate Units via Stereoselective Hydrogenation of Optically Active Cycloheptatriene

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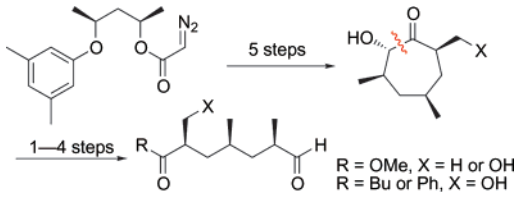
Received August 18, 2004

ABSTRACT

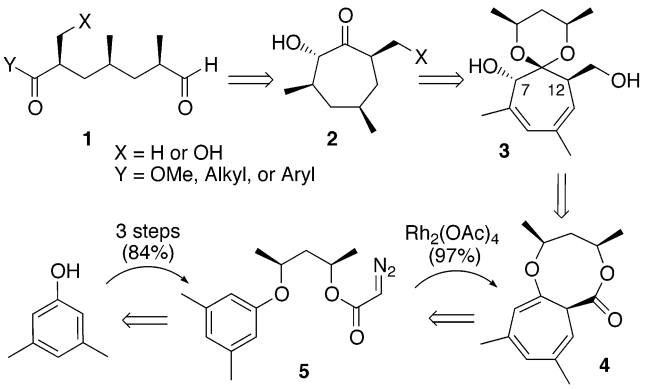


Optically active polypropionate units were synthesized in 9–11 steps from 3,5-dimethylphenol. The sequence consists of the BUchner reaction controlled by a chiral 2,4-pentanediol tether and diastereoselective hydrogenation over Raney nickel.

Polyketides are ubiquitous natural products including many important antibiotics such as macrolides. The structure of the skipped methyl groups in a polyketide is biologically synthesized by the propionyl-CoA or α-methylmalonyl-CoA cycle, which constructs chiral centers in a variety of patterns under strict control.[1] For the synthesis of such compounds, many elegant stereocontrolled reactions have been developed, but the reactions controlling the formation of multichiral centers are still limited.[2]

Optically active 2,4-pentanediol (PD) is a popular chiral auxiliary and exhibits strict stereocontrollability when it is used as a tether connecting two reactants.[3] The Büchner reaction is one of the successful examples that produces many chiral cycloheptatriene derivatives in optically active forms.[4] In the present study, we planned to use such a compound, **4**, prepared from 3,5-dimethylphenol via the PD-tethered Büchner reaction of **5**, to synthesize a chiral building block **1** (X = H or OH) that corresponds to a deoxytripropionate unit (Scheme 1). A key step of this procedure is the hydrogenation of **3** at the conjugated diene to generate two

Scheme 1. Retrosynthesis of Chiral Polypropionate Unit **1** via Optically Active Cycloheptatriene **4**



(1) *Comprehensive Natural Products Chemistry*; Sankawa, U., Ed.; Elsevier: Amsterdam, 1999; Vol. 1. *Macrolide Antibiotics*; Omura, S. Ed.; Academic Press: Amsterdam, 2002.

(2) A typical exception is desymmetrization of *meso*-compounds. For a review, see: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096−1109.

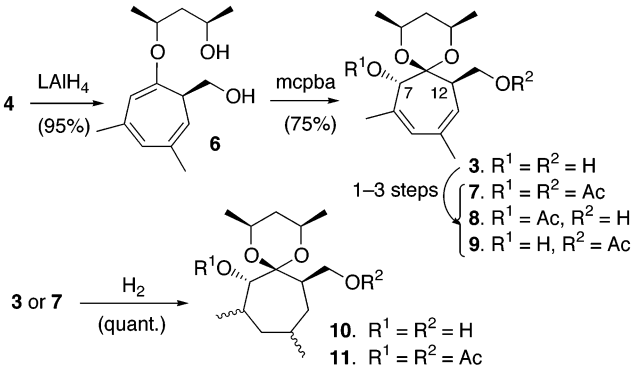
(3) Sugimura, T. In *Recent Research Developments in Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: Trivandrum, 1998; Vol. 2, pp 47−53.

10.1021/ol0483596 CCC: $27.50
Published on Web 10/22/2004

chiral centers stereocontrolled by the substituents at the 7- and/or 12-positions, and thus these chiral centers must also be stereoselectively generated.

The optically active **4** was prepared by the reported method[5] and converted to **6** (>99% ee) by reduction in 95% yield (Scheme 2). The oxidation of **6** by the addition of

Scheme 2. Hydrogenation of the Conjugate Diene



MCPBA in dichloromethane at −40 °C was sufficiently stereocontrolled to give **3** as a single diastereomer (>99% pure, up to 75% yield, 50−60% on a large scale).[6] Since the oxidation introducing 7-OH and the acetal formation occur at the same stereoface (*anti* to the 12-hydroxymethyl group), the hydroxy group in the PD part of **6** should effectively direct the peracid to the reaction site.[7]

The hydrogenation of **3** can in principle produce four diastereomers of **10**, but when Raney nickel, Pt on alumina, or Pd on carbon was employed as a catalyst, only two isomers, **10a** and **10b**, were produced in a quantitative yield. Table 1 shows the product selectivity of the hydrogenation

Table 1. Stereochemical Purity of the Product (100 × **10a**/(**10a** + **10b**))[a] for the Hydrogenation of **3** and Its Analogues **7**−**9** in Different Solvents

substrate (R^1, R^2)	catalyst	MeOH	EtOAc	hexane
3 (H, H)	RNi	93	98	96
	Pt/Al_2O_3	97	88	91
	Pd/C	83	83	86
7 (Ac, Ac)	RNi	69	76	76
	Pt/Al_2O_3	68	86	88
	Pd/C	75	78	80
8 (Ac, H)	RNi	77	84	87
9 (H, Ac)	RNi	90	94	98

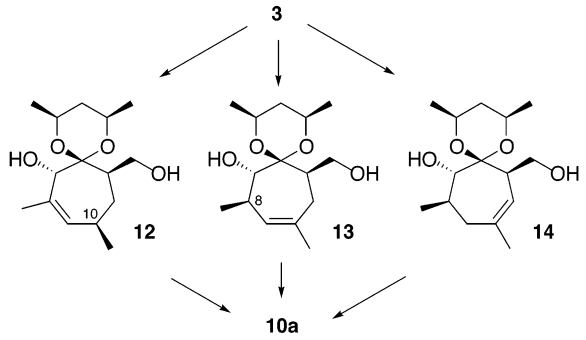
[a] Determined by a GLC analysis after conversion to **11**.

of **3** and its hydroxy-protected substrates, **7**−**9**, in methanol, ethyl acetate, or hexane.

For the hydrogenation of **3**, the stereochemical purity of the produced **10** (100 × **10a**/(**10a** + **10b**)) is over 80% in all cases, and the Ni and Pt catalysts provided better selectivity than does the Pd catalyst. When both hydroxy groups were protected, **7** showed lower selectivities, suggesting that the effects of the hydroxy group(s) decrease in the order of Ni > Pt > Pd.[8] For the Ni-catalyzed hydrogenation, the results with **8** and **9** suggest that the 7-OH (R^1 = H) group has greater effects on the selectivity than does the 12-CH_2OH group (R^2 = H). The selectivity with the 7-OH substrates (**3** and **9**) over the Ni catalyst reaches 98% purity (96% diastereomeric excess of **10a**) in an optimum solvent.

When the hydrogenation process was monitored by ^{1}H NMR under one of the best conditions (**3**/Ni/EtOAc), three mono-ene intermediates were detected in a similar quantity during the very early stage (<5% consumption of **3**). One of the intermediates was not accumulated during the hydrogenation, whereas the other two intermediates and **10a** increased at a similar rate until the 50% consumption of **3**. In further reaction, the intermediates decreased with an increase in **10a**. The minor mono-ene isomer should be a reactive intermediate, which was isolated and assigned as **12**, where the stereochemistry at the 10-position was determined by NOE between H-10 and H-12 (Scheme 3).

Scheme 3. Three Intermediates during the Hydrogenation of **3** to Give **10a**



Because the hydrogenation of all of the intermediates gave **10a**, the structure of the other two intermediates should be **13** and **14**, where the stereochemistries at the 8-position are determined by the chemical conversion of **10a**, as will be shown later. It should be worth noting that all three sets of the two-step reaction pathways (six independent reactions)

(4) Sugimura, T.; Nagano, S.; Tai, A. *Chem. Lett.* **1998**, 45−46. Sugimura, T.; Hagiya, K.; Sato, Y.; Tei, T.; Tai, A.; Okuyama, T. *Org. Lett.* **2001**, *3*, 37−40. Sugimura, T.; Ohuchi, N.; Kagawa, M.; Hagiya, K.; Okuyama, T. *Chem. Lett.* **2004**, *33*, 404−405.

(5) Sugimura, T.; Nishida, F.; Tei, T.; Morisawa, A.; Tai, A.; Okuyama, T. *Chem. Commun.* **2001**, 2180−2181.

(6) Stereochemistry and purity at the 7-position of **3** was determined by NMR in comparison with a 7,12-*syn*-isomer of **3**. Details of the diastereomer preparation will be published elsewhere.

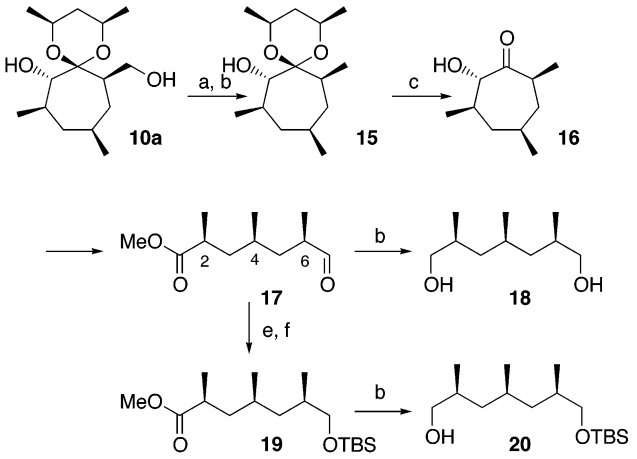
(7) Sugimura, T.; Nishiyama, N.; Tai, A. *Tetrahedron: Asymmetry* **1993**, *4*, 43−44. Sugimura, T.; Iguchi, H.; Tsuchida, R.; Tai, A.; Nishiyama, N.; Hakushi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1007−1013.

(8) Brown, J. M. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 7. pp 4317−4333. Bartok, M. *Stereochemistry of Heterogeneous Metal Catalyst*; Wiley: Chichester, 1985; pp 53−290. Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley: New York, 2001; pp 64−147. Rylander, P. N. *Hydrogenation Methods*; Academic Press: London, 1985; pp 29−52.

are stereocontrolled in the same direction, and the present high stereoselectivity could not have been achieved if any one of the six reaction steps could not be controlled.[9] Such a strict stereocontrollability through the hydrogenation is attributable to the effective cooperation of the steric and polar interactions between the substrate and the catalyst surface; the 7-OH is fixed at the axial position to contribute the polar interaction, while the 12-CH_2OH is equatorially placed to force one of the reaction faces open. The difference between the 7- and 12-substituents in their conformations must be due to the difference in the steric hindrance caused by the acetal ring.[10]

The stereochemically pure **10a** obtained by recrystallization was converted to **15** by mono-methanesulfonylation (73%) and lithium aluminum hydride reduction (91%) (Scheme 4). The hydrolysis of **15** by the TsOH catalysis in

Scheme 4. Asymmetric Synthesis of 2,4,6-Trimethylheptanoic Acid Derivatives[a]



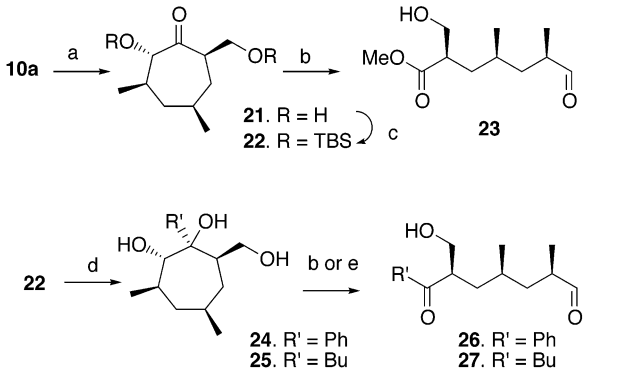
[a] Reagents and conditions: (a) $MsCl/NEt_3/CH_2Cl_2$ (73%); (b) $LiAlH_4$/ether (65% for **18**); (c) TsOH/THF/H_2O (79%); (d) Pb(OAc)4/benzene/MeOH (74%); (e) $NaBH_4$/MeOH (94%); (f) TBSCl/imidazole/DMF (quant).

THF/H_2O resulted in **16** (79%), the ^{1}H NMR of which showed no epimerization unless the reaction time was prolonged. Oxidative cleavage of the purified **16** with lead tetraacetate in benzene/methanol[11] gave (+)-**17** as the sole product (74%).

The stereochemistries of **17** are 2*S*,4*S* because those positions correspond to 12 and 10 of **10a**, respectively. Since **18** obtained by the reduction of **17** is a symmetric compound showing only six carbons in the NMR, the 6-position of **17** is determined to be *R*, and thus two methyl groups of the reactant **10a** are both *syn* to the 12-hydroxymethyl as shown in Scheme 4. The stereochemical purity of **17** was confirmed to be >99% after conversion to **20** via **19**. That is, the obtained **20** showed a single peak based on the chiral GLC analysis, whereas the racemic **20** prepared from **18** gave two separate peaks.[12] Overall, the optically active **17** was synthesized in 11 steps from 3,5-dimethylphenol in 22% yield.[13]

To disclose the diversity of **10a**, the ring-cleavage step was performed prior to the removal of the hydroxy group at the 12-methylene. When **21** obtained by the hydrolysis of **10a** was treated with lead tetraacetate, the ring cleavage again proceeded without isomerization to give the diastereomerically pure **23** in 80% yield (Scheme 5). During this conversion, the hydroxymethyl was found to survive without protection. The product **23** can be a synthon not only for compounds having a hydroxymethyl group but also for those having methylene or substituted methyl groups. Switching of the chirality at the 2-position of **23** by changing the terminal position from the ester to the hydroxymethyl also becomes possible.

Scheme 5. Ring Cleavage Prior to Removal of the Hydroxy Group[a]



[a] Reagents and conditions: (a) TsOH/THF/H_2O (88%); (b) $Pb(OAc)_4$/benzene/MeOH (80% for **23**, 91% for **26**); (c) TBSCl/imidazole/DMAP (99%); (d) PhLi (58%) or BuLi (78%), and then TBAF/THF (95% or 50%); (e) $NaIO_4$/AcOH (92% for **26**, 87% for **27**).

An alternative use of **10a** as a chiral synthon is that another unit (R′) is introduced prior to the ring cleavage. The two hydroxy groups of **21** were first protected by the TBS group (**22**, 99%). When **22** was treated with phenyllithium in ether at −78 °C, the adduct was produced as a single stereoisomer (58%), which was converted to **24** by deprotection (95%). The ^{1}H NMR spectrum of this adduct is noteworthy because

(9) The regioselectivity of the hydrogenation of the conjugated diene is generally poor to moderate. For an example, see: Kazanskii, B. A.; Gostunskaya, I. V.; Granat, A. M. *Izv. Akad. Nauk SSSR, Otdel. Kim. Nauk* **1953**, 670−674. See also ref 8.

(10) The stable conformations of **3**, **12**, **13**, and **14** were estimated by MM3 calculations. Their structures are given in Supporting Information.

(11) Baer, E. *J. Am. Chem. Soc.* **1942**, *64*, 1416−1421.

(12) Note that the epimerization of **16** at the α-ketol part during the formation and the reaction results in an exchange of the keto and alcohol positions to reduce the stereochemical purities of its derivatives.

(13) Compound **17** can be used for the syntheses of, e.g., borrelidin,[a] lardolure,[b] TCM-151,[c] and verucopeptin.[d] (a) Berger, J.; Jampolsky, L. M.; Goldberg, M. W. *Arch. Biochem*, **1949**, *22*, 476−478. (b) Kuwahara, Y.; Yen, L. T. M.; Tominaga, Y.; Matsumoto, K.; Wada, Y. *Agric. Biol. Chem.* **1982**, *46*, 2283−2291. (c) Kohno, J.; Nishio, M.; Sakurai, M.; Kawano, K.; Hiramatsu, H.; Kameda, N.; Kishi, N.; Yamashita, T.; Okuda, T.; Komatsubara, S. *Tetrahedron* **1999**, *55*, 7771−7786. (d) Sugawara, K.; Toda, S.; Moriyama, T.; Konishi, M.; Oki, T. *J. Antibiotics* **1993**, *46*, 928−935.

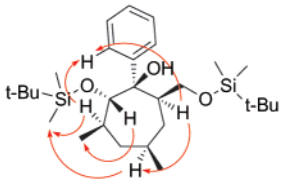


Figure 1. Selected H−H NOE signals observed for the TBS-protected **24**.

all of the ring protons are observed as separate peaks. The result of the NOESY spectra shown in Figure 1 not only indicates the stereochemistry of the nucleophilic addition but also confirms all of the other stereochemistries. In this case, the ring cleavage to give **26** could be performed both by sodium periodate with acetic acid (92%) and by lead tetraacetate (91%). The same procedure, except for the use of butyllithium instead of phenyllithium, afforded the alkyl-substituted **25** (78% for two steps), and the ring cleavage with sodium periodate/acetic acid gave the stereochemically pure **27** in 87% yield.

In the present study, we have demonstrated that the optically active cycloheptatriene prepared from 3,5-dimethylphenol can be converted into several deoxy polypropionate units under efficient stereocontrol. Judging from the availability of phenol analogues, the present procedure can be extended to the synthesis of many other optically active compounds.

Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0483596