ORGANIC LETTERS

2000
Vol. 2, No. 22
3449−3451

Desymmetrization of *meso*-Dialdehydes with Optically Active Cyclopentadienyldialkoxyallyltitanium Complexes

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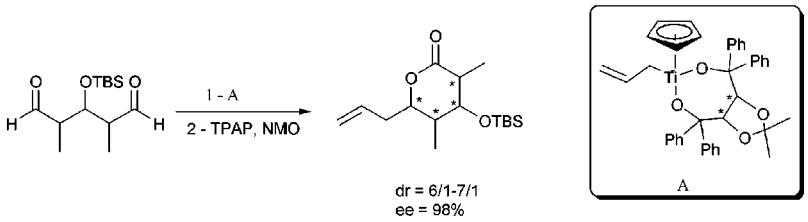
Received March 12, 2000 *(Revised Manuscript Received August 10, 2000)*

ABSTRACT



Optically active cyclopentadienyldialkoxyallyltitanium complexes have been employed for the desymmetrization of *meso*-dialdehydes. Allylation of these dialdehydes and subsequent oxidation afford chiral lactones with good diastereoselectivity and excellent enantioselectivity.

The stereochemical complexity of polyketide natural products has ensured that, despite intense research, the need for new methodology for their construction remains as great as ever. Classically, the contiguous stereocenters in polyketide systems have been formed sequentially, via processes such as iterative aldol[1] or allylmetal[2] additions to aldehyde intermediates. In recent years, however, the desymmetrization of *meso* systems both by enzymatic[3] and chemical methods[4] has emerged as a promising but less explored alternative.

In looking for routes to prepare advanced stereotriads, our interest was drawn to the dialdehyde **1**.[5] It has previously proved possible to effect the desymmetrization of this dialdehyde through Horner−Wadsworth−Emmons[6] and aldol transformations involving chiral auxiliaries.[7]

Our approach to the formation of lactol **2** via desymmetrization of the *meso*-dialdehyde **1** employs the Duthaler−Hafner[8] allyltitanium complexes (*R*,*R*)-**I** and (*S*,*S*)-**II** (Scheme 1). Duthaler et al. have shown that the (*R*,*R*)-**I** and (*S*,*S*)-**II** complexes will allylate with high selectivity at the *si* and *re* faces, respectively, of prochiral aldehydes. We were convinced of the pratical utility of these complexes in this desymmetrization for two reasons. First, being derived from either D- or L-tartrate, both enantiomeric complexes are readily available. Second, the low Lewis acidity of the titanium complexes should ensure their compatibility with sensitive dialdehydes.[9]

(1) (a) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287.

(2) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(3) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769.

(4) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.

(5) Harada, T.; Matsuda, Y.; Wada, I.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21.

(6) (a) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802. (b) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P. O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284.

(7) (a) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardellini, G.; *Tetrahedron Lett.* **1995**, *36*, 4413. (b) De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169

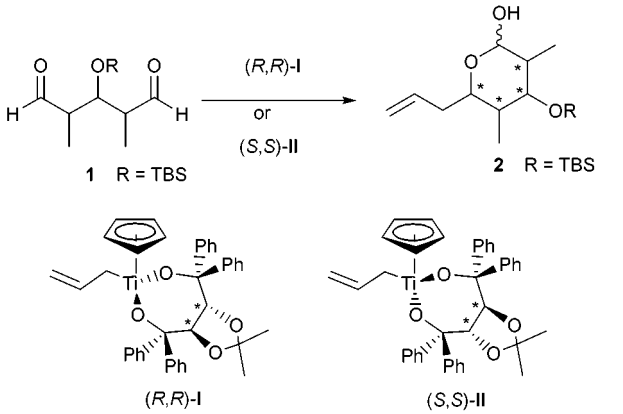
(8) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807.

(9) Reetz, M. T. In *Organometallics in Synthesis—A Manual*; Schlosser, M., Ed.; John Wiley & Sons: New York, 1994; Chapter 3, p 195.

(10) TADDOL refers to the ligand *trans*-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol.

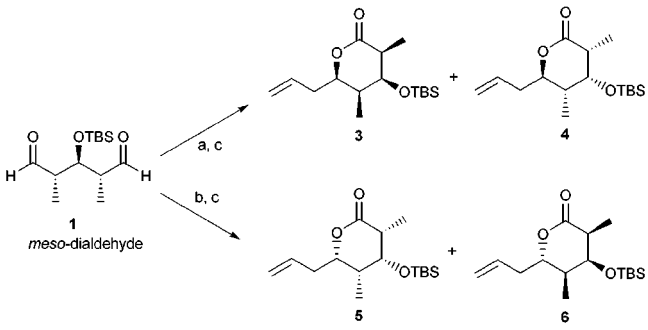
10.1021/ol0057434 CCC: $19.00
Published on Web 10/06/2000

Scheme 1



The titanium complexes (*R*,*R*)-**I** and (*S*,*S*)-**II** were formed in ether by transmetalation at 0 °C of allylmagnesium chloride with the appropriate cyclopentadienyl-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′-titanium chloride precursors. Subsequent cooling to −78 °C and addition of the aldehyde was followed after 3 h by quenching with water. Hydrolysis of the resulting titanium alkoxide species over 12 h gave a mixture of lactol **2** and liberated TADDOL.[10] Chromatography of the lactol proved laborious, and it was found that tetrapropylammonium perruthenate (TPAP)[11] oxidation allowed facile purification of the stable lactones (Scheme 2).

Scheme 2[a]



[a] (a) (*S*,*S*)-**II**, −78 °C, ether; (b) (*R*,*R*)-**I**, −78 °C, ether; (c) TPAP, NMO, CH_2Cl_2.

Thus, addition of the (*S*,*S*)-**II** complex with aldehyde **1** and subsequent oxidation led to the lactones **3**[13] and **4** in excellent yield and with good diastereoselectivity (Table 1, entry 1). Similarly, the use of the (*R*,*R*)-**I** complex produced the opposite two enantiomers **5**[13] and **6** in similar proportions, although in substantially reduced yield (entry 2). Chiral GC

Table 1

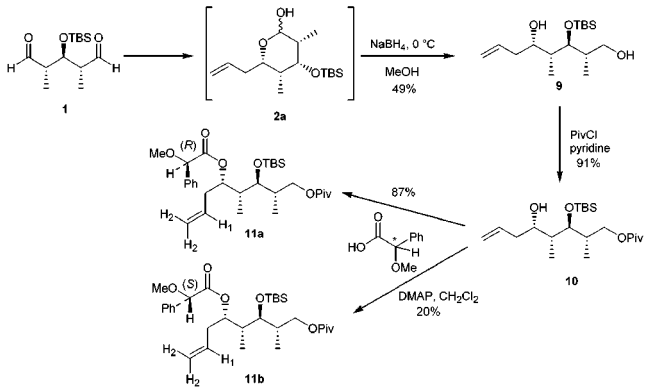
entry	complex	equiv of complex[a]	scale (mmol **1**)	products	ratio	yield[b] (%)	ee[c]
1	(*S*,*S*)-**II**	0.5	0.38	**3**/**4**	6/1	83	>98
2	(*R*,*R*)-**I**	0.5	0.26	**5**/**6**	7/1	48	>98
3	(*R*,*R*)-**I**	0.9	1.50	**5**/**6**	7/1	62	
4	(*R*,*R*)-**I**	0.5	3.00	**5**/**6**	7/1	56	

[a] Relative to **1**. [b] Isolated after oxidation. [c] For major isomer, determined by chiral GC. See ref 12.

analysis showed clearly that both complexes operated with effectively total enantioselectivity. The diastereolectivity was unaffected when the ratio of aldehyde to (*R*,*R*)-**I** was increased (entry 3). At the same time, a 10-fold increase in the scale of the reaction was also possible, without significant loss in yield or selectivity (entry 4).

The absolute configuration of the C-3 center in compound **5** was achieved by transforming the lactol **2a** into the *O*-methylmandelates **11a** and **11b** and analysis of their ^{1}H NMR spectrum (Scheme 3). Lactol **2a** was reduced to **9**

Scheme 3



($NaBH_4$, MeOH, 0 °C). Esterification of the primary alcohol **9** with pivaloyl chloride led to **10**, which was transformed to **11a** and **11b** by esterification of the secondary alcohol with (*R*)- and (*S*)-*O*-methylmandelic acid, respectively.[14] The spectrum of **11a** shows an upfield shielding of 0.3 ppm for the protons H_1 and H_2. On the contrary, no upfield shielding was observed for these protons in compound **11b**. These observations allow us to assign the C-3 (*S*)-configuration in compound **5**.

Furthermore, evidence for the relative stereochemistry of the product **5** was obtained by treatment of compound **10**

(11) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

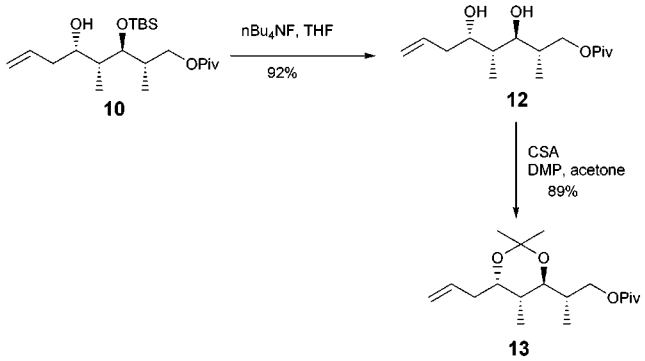
(12) Chiral GC−MS was performed using a Hewlett-Packard series II 5890 with a custom-made F5-20% dimethylbutylsilane TB50 in SES column.

(13) **3** and **5**: IR (neat, cm^{-1}) 1752, 1736, 1714, 1474, 1459, 1438, 1420, 1363, 1260; ^{1}H NMR ($CDCl_3$, 300 MHz) 5.90−5.76 (m, 1H), 5.20−5.10 (m, 2H), 4.29 (ddd, J = 8.3, 5.9, and 3.4 Hz, 1H), 4.10 (dd, J = 6.8 and 5.9 Hz, 1H), 2.76 (quintet, J = 7.2 Hz, 1H), 2.65−2.55 (m, 1H), 2.37−2.27 (m, 1H), 2.21 (ddd, J = 7.2, 5.8, and 3.4 Hz, 1H), 1.26 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H), 0.93 (s, 9 H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.4 (s), 133.4 (d), 117.9 (t), 77.0 (d), 70.3-(d), 40.2 (d), 38.3 (d), 36.3 (t), 25.(q), 18.1 (s), 12.7 (q), 7.9 (q), −4.5 (q), −4.8 (q); HRMS calcd for $C_{16}H_{31}O_3Si$ (MH^+) 299.2042, found 299.2037.

(14) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

with tetrabutylammonium fluoride and subsequent protection of the diol **12** with 2,2-dimethoxypropane in the prescence of CSA in acetone, which afforded the acetonide **13** (Scheme 4).[15,16]

Scheme 4



The observed diastereopreference for lactones **3** and **5** may be explained by careful consideration of the stereocontrol exerted by the latent stereocenters in the *meso*-dialdehyde **1**. The nucleophile is presented with four possible modes of attack at the dialdehyde. In considering the (*R*,*R*)-**I** complex, *si* face selectivity would equally favor each of the two approaches shown in Figure 1, since the allyltitanation of

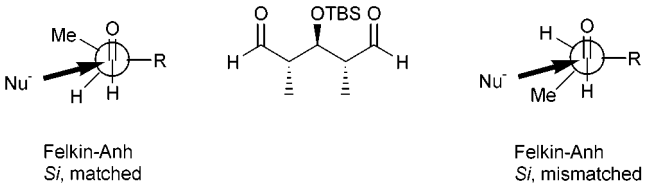


Figure 1.

aldehydes possessing α-stereocenters by (*R*,*R*)-**I** and (*S*,*S*)-**II** has been shown to closely follow the Felkin-Anh transition state, in accord with our independent stereochemical analysis.

In conclusion, we have demonstrated that a combination of the *meso*-dialdehyde **1** with cyclopentadienyldialkoxyallyltitanium complexes (*R*,*R*)-**I** and (*S*,*S*)-**II** allows access to each of the enantiomeric lactones **3** and **5** with excellent enantioselectivity. The relative stereochemistry of the substituents in lactone **5** was demonstrated via formation of the acetonide derivative **13**, and the absolute configuration of the newly formed center was shown by ^{1}H NMR analysis of the corresponding *O*-methylmandelates.

Acknowledgment. We thank Dr. R. O. Duthaler for a generous gift of cyclopentadienyl[(4*S*,*trans*)- and cyclopentadienyl-[(4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride and Pr. J. A. Marshall for useful discussions. M.E.P. thanks the CNRS for a grant.

OL0057434

(15) The stereochemistry of *syn*- and *anti*-1,3-diol acetonides can be assigned from the ^{13}C chemical shifts of the acetal methyl groups and the acetal carbon. In general, *syn*-1,3-diol acetonides have methyl shifts at 19 and 30 ppm and acetal shifts at 98.5 ppm, whereas the *anti* acetonides have methyl shifts at 24.5 ppm and acetal shifts at 100.5 ppm. The values for **13**[16] are 25.2, 23.3, and 100.5 ppm, respectively. Rogers, B.; Rychnowsky, S. D.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(16) Compound **13**: $[\alpha]_D = -4.5$ (*c* 0.28, $CHCl_3$); IR (neat, cm^{-1}) 1750, 1505, 1410, 1180; ^{1}H NMR ($CDCl_3$, 300 MHz) 5.86−5.72 (m, 1H), 5.15−5.02 (m, 2H), 4.19−4.14 (m, 1H), 4.02−3.96 (m, 1H), 3.88−3.81 (m, 1H), 3.22 (dd, J = 6.6 and 5.9 Hz, 1H), 2.28−2.18 (m, 1H), 2.14−2.07 (m, 1H), 1.98−1.89 (m, 1H), 1.88−1.79 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.20 (s, 9 H), 1.01 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.5 (s), 134.9 (d), 116.4 (t), 100.3 (s), 76.1(s), 76.0 (d), 68.8 (d), 65.8 (t), 36.9 (d), 36.6 (d), 34.9 (t), 27.1 (q, *t*-Bu), 25.2 (q), 23.2 (q), 13.8 (q), 12.4 (q); MS(IE) *m*/*z* 312 (M^+), 297 (14), 213 (6), 184 (9), 173 (19), 111(15), 82 (100), 57 (46).