

STEREOSELECTIVE ALDOL REACTIONS USING $TiCl_4$ AS STEREOCHEMICAL TEMPLATE

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Abstract: $TiCl_4$ mediated aldol condensations establish multiple contiguous chiral centers in an almost complete enantio- and diastereoselective way.

Due to its structural features (chirality and the possibility of β chelation) 3-benzyloxy-2-methylpropionaldehyde has been widely used in organic synthesis,¹ and its optically active forms are important intermediates in the total synthesis of natural products.² Both enantiomers have usually been prepared from β -hydroxyisobutyric acid,³ and more recently by asymmetric synthesis.⁴

Here we report a straightforward (4 step) enantioselective synthesis of (4), fulfilling the following requirements: a) enantiomeric excess $> 90\%$, and high chemical yield b) both enantiomers of the chiral inductor are inexpensive, commercially available materials c) the chiral inductor can be recycled d) the absolute configuration of the reaction product is easily predictable on the basis of the reaction mechanism.

$TiCl_4$, which usually ligates two electron-donating molecules to form cis-octahedral, six-coordinate complexes, served as a stereochemical template for the asymmetric aldol-type reaction. Trimethylorthoformate was used as the first ligating molecule, the second donor being the NMe_2 group of N-methyl ephedrine. Therefore, using the E silyl ketene acetal derived from 1R, 2S-N-methylephedrine-O-propionate, the reaction occurs on the six-coordinate metal with formation of Me_3SiCl , and of the C-C bond in a stereoselective way (see transition state model A).^{5,6} Inspection of the space-filling model of transition state B reveals the unfavorable steric interaction between the methyl of the propionate and the ephedrine residue, which is probably responsible for the observed selectivity.

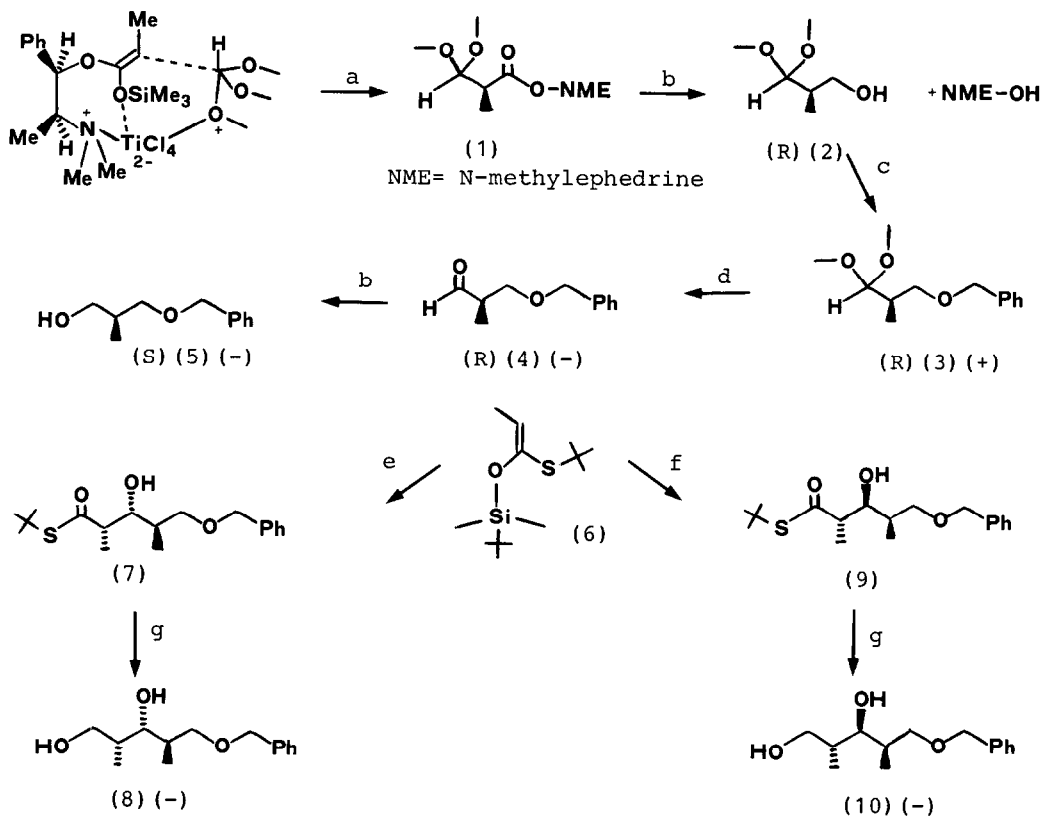
N-methylephedrine (1R,2S) was treated with CH_3CH_2COCl in CH_2Cl_2 to give the O-propionate (100%). LDA enolization (THF, $-78^\circ C$) and Me_3SiCl trapping ($-78^\circ C$)

gave the silyl ketene acetal (95%; E-Z \geq 95:5), which was worked-up by evaporation without water-quenching. Addition of 1 mol.equiv. of the silyl ketene acetal in CH_2Cl_2 to 1 mol.equiv. of the TiCl_4 -orthoformate complex at -78°C in CH_2Cl_2 , gave the condensation product (1) in 62% yield and with high stereoselectivity (\geq 20:1 by 300 MHz ^1H NMR spectroscopy). Reduction (LAH, Et_2O , RT) of the crude condensation product gave a mixture which was separated by fractional distillation (16 mmHg) to give the alcohol (2) (95%) and optically pure N-methylephedrine which could be recycled. Benzoylation of (2) (NaH, PhCH_2Br , Bu_4NI cat., THF) gave (3) (90%) ($[\alpha]_D^{25} = +7.6^\circ$ c 1.2, CHCl_3). Hydrolysis of (3) ($\text{AcOH-H}_2\text{O}$ 1:1, RT, 20 h) gave (R) (4) ($[\alpha]_D^{25} = -25.8^\circ$ c 1.0, CHCl_3 ; lit.^{4a} + 28.4° c 1.56, CHCl_3) in 80% yield. Reduction of (R) (4) (LAH, Et_2O , 0°C) gave (S) (5) (95%) ($[\alpha]_D^{25} = -16.1^\circ$ c 1.4, CHCl_3 ; lit.^{2b} +17.2° c 3.24, CHCl_3 ; $[\alpha]_D^{25} = -4.82^\circ$ c 1.4, EtOH ; lit.^{4b} + 5.3° c 2.2, EtOH) which was shown to be 91% enantiomerically pure through its diastereomeric Mosher esters (21:1).^{2c}

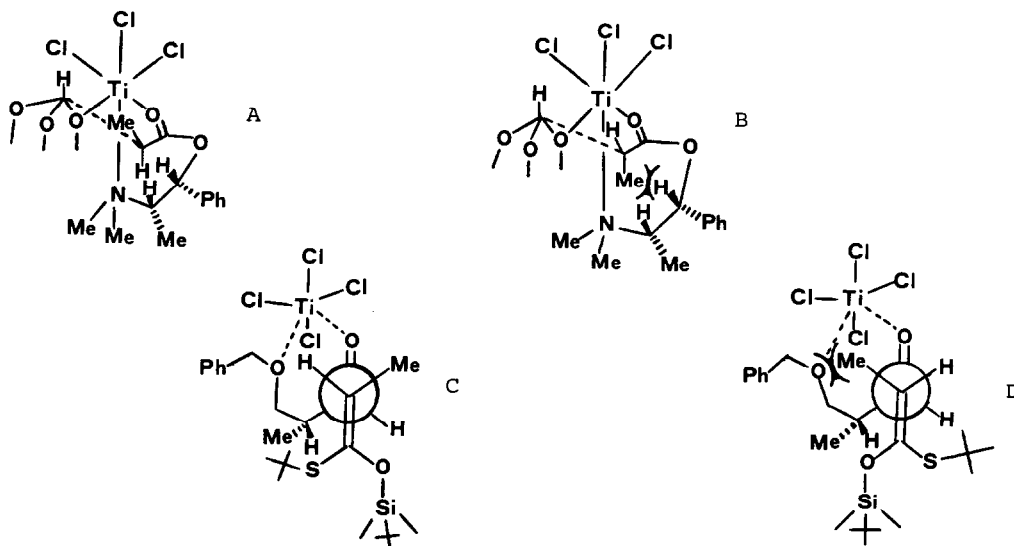
The aldehyde was then reacted with the thioester silyl ketene acetal (6)^{7,8} and TiCl_4 (CH_2Cl_2 , -78°C) to give compound (7), a monensin synthetic intermediate,^{2a} in 67% isolated yield and > 99% stereoselectivity (capillary VPC, ^{13}C NMR). As shown by the transition state models C and D, the conformational changes forced by the Lewis acid (chelation control) disfavour D (gauche steric repulsion between Me and the aldehyde residue). Reduction of (7) (Raney-Ni, H_2 , MeOH) gave the known alcohol (8) ($[\alpha]_D^{25} = -32.7^\circ$ c 1.0, CHCl_3 ; lit.^{2b} + 38.4° c 0.94, CHCl_3) in 70% yield. The observed optical purity of (8) (85%), which could result from a slight racemization of (4) during the TiCl_4 -mediated condensation, was confirmed via ^1H NMR spectroscopy (200 MHz) of its stereoisomeric Mosher esters.

Using a non-chelating Lewis acid ($\text{BF}_3\text{-OEt}_2$ 2 mol. equiv., CH_2Cl_2 , -78°C) three stereoisomers (77%, 14%, 9%, capillary VPC, ^{13}C NMR) were obtained (75% yield).⁸ The major was characterized as compound (9), and reduced (Raney-Ni, H_2 , MeOH) to the known alcohol (10).^{2b}

Therefore, using TiCl_4 as a stereochemical template, three contiguous stereo centers were established with high selectivity.⁹



a) $\text{CH}_2\text{Cl}_2, -78^\circ\text{C}$ b) $\text{LAH}, \text{Et}_2\text{O}$ c) $\text{NaH}, \text{PhCH}_2\text{Br}, \text{Bu}_4\text{NI cat.}, \text{THF}, \text{RT}$ d) $\text{AcOH}, \text{H}_2\text{O}, \text{RT}$
 e) $\text{TiCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ\text{C}$ f) 2 eq. $\text{BF}_3\text{-OEt}_2, \text{CH}_2\text{Cl}_2, -78^\circ\text{C}$ g) $\text{Raney-Ni W1}, \text{H}_2, \text{MeOH}, \text{RT}, 0.5\text{h}$



NOTES AND REFERENCES

- 1) a) C.H. Heathcock, S.I.Kiyooka, T.A.Blumenkopf, J.Org.Chem., 1984, 49, 4214, and reference 6 quoted therein; b) M.T. Reetz, K. Kessler, A. Jung, Tetrahedron, 1984, 40, 4327; c) S.J. Danishefsky, W.H. Pearson, D.F. Harvey, J.Am.Chem.Soc., 1984, 106, 2455, 2456; d) S.J. Danishefsky, W.H. Pearson, D.F. Harvey, C.J. Maring, J.P. Springer, J.Am.Chem.Soc., 1985, 107, 1256; e) M.T. Reetz, Angew.Chem.Int.Ed.Engl., 1984, 23, 556; f) W.C. Still, J.A. Schneider, Tetrahedron Letters, 1980, 1035.
- 2) a) D.B. Collum, J.H. McDonald III, W.C. Still, J.Am.Chem.Soc., 1980, 102, 2118 (monensin); b) H. Nagaoka, Y. Kishi, Tetrahedron, 1981, 37, 3873 (rifamycin S); c) A.I. Meyers, e.a., J.Am.Chem.Soc., 1983, 105, 5015 (maysine).
- 3) a) C.T. Goodhue, J.R. Schaeffer, Biotechnol. Bioeng., 1971, 13, 203; b) N. Cohen, W.F. Eichel, R.J. Lopresti, C. Neukom, G. Saucy, J.Org.Chem., 1976, 41, 3505; c) W. Choy, P. Ma, S. Masamune, Tetrahedron Letters, 1981, 22, 3555; d) Q. Branca, A. Fischli, Helv. Chim. Acta, 1977, 60, 925.
- 4) a) W.R. Roush, M.A. Adam, S.M. Peseckis, Tetrahedron Letters, 1983, 1377; b) for the enantioselective synthesis of alcohol (5) see: D.A. Evans, M.D. Ennis, D.J. Mathre, J.Am.Chem.Soc., 1982, 104, 1737.
- 5) For an application of this new method to the enantioselective synthesis of anti α -methyl- β -hydroxyesters, see: C. Gennari, A. Bernardi, L. Colombo, C. Scolastico, J.Am.Chem.Soc., submitted. Further extension of this method to other reactions is under current investigation.
- 6) The crystal structure of a cis-octahedral, six-coordinate titanium complex containing a seven-membered ring chelate structure has been recently reported: T. Pool, J.O. Metter, G. Helmchen, Angew.Chem.Int.Ed.Engl., 1985, 24, 112.
- 7) C. Gennari, A. Bernardi, S. Cardani, C. Scolastico, Tetrahedron Letters, 1985, 797; C. Gennari, A. Bernardi, G. Poli, C. Scolastico, Tetrahedron Letters, 1985, 2373.
- 8) In both the TiCl_4 - and the BF_3 -mediated reactions, both the (E) silyl ketene acetal (6) and the (Z) silyl ketene acetal gave almost the same results (yield and selectivity). For a discussion on the stereoconvergence of thioester silyl ketene acetals see ref.7 of this paper.
 TiCl_4 or $\text{BF}_3\text{-OEt}_2$ were added dropwise to a stirred mixture of aldehyde (4) and silyl ketene acetal (6) at -78°C in CH_2Cl_2 . After 1 h at -78°C the mixture was quenched and worked-up as usual.
- 9) Satisfactory spectral and analytical data were obtained on all reported compounds. The $[\alpha]_D$ were compared to the highest literature values (see text). The $[\alpha]_D$ values reported are the following: (R) (4) -28.17° (c 1.4, CHCl_3) (ref.2c); (S) (4) $+28.4^\circ$ (c 1.56, CHCl_3) (ref.4a); (R) (5) $+17.2^\circ$ (c 3.24, CHCl_3) (ref.2b); (R) (5) $+16.5^\circ$ (c 1.05, CHCl_3) (ref.4a); (R) (5) $+5.2^\circ$ (c 1.46, EtOH) (ref.4a); (S) (5) $+5.3^\circ$ (c 2.2, EtOH) (ref.4b); (S) (5) $+4.97^\circ$ (c 0.93, EtOH) (ref.3d); (S) (5) -11.3° (c 16.05, CHCl_3) (ref.2c). The last three values are not consistent with our data.

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