Tetrahedron Letters, Vol.32, No.51, pp 7517-7520, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Catalytic Enantioselective Synthesis of a Key Intermediate for the Synthesis of Prostanoids

E. J. Corey, Nobuyuki Imai and Stanislaw Pikul

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *A route has been demonstrated for the enantioselective synthesis of prostanoids from achiral starting materials by the use of chiral catalysts of the molecular robot class.*

Some years ago we reported the first general synthesis of prostanoids from bicyclo[2.2.1]heptenone intermediates (**1**)[1] which were synthesized as racemates by a Diels-Alder addition of a 5-(alkoxymethyl)-1,3-cyclopentadiene with a ketene equivalent such as 2-chloroacrylonitrile (Cu^{+2} catalysis)[1a] or 2-chloroacrylyl chloride.[1c] Chiral prostanoids were obtained by conversion of **1** to acid **2** and resolution.[1b] Subsequently, chiral **1** was prepared enantioselectively by $AlCl_3$-catalyzed Diels-Alder reaction of the reactive species **3**, involving the 8-phenylmenthol controller group,[2] and transformed into the enantiomerically pure iodo lactone **4** after recrystallization. We now report a further evolution of this approach which takes advantage of a *catalytic* enantioselective Diels-Alder reaction as the initial step for the synthesis of enantiomerically pure **4** from achiral reactants.

The use of chiral catalysts such as **5** for enantioselective Diels-Alder reactions has been described recently.[3] Thus, reaction of 5-(benzyloxymethyl)-1,3-cyclopentadiene (**6**) and 3-acrylyl-1,3-oxazolidin-2-one (**7**) in the presence of 10 mole % of the (*S,S*)-catalyst **5** in CH_2Cl_2 at -78 °C for 18 h afforded the adduct **8** in 93% yield and > 95% ee. The chiral bis-sulfonamide from which catalyst **5** was made was recovered for reuse. The adduct **8** was converted to the crystalline, enantiomerically pure iodo lactone **4** by the following sequence. Treatment of **8** with aqueous lithium hydroxide–H_2O_2[4] provided the corresponding acid (100%) which was transformed into the ethyl ester (**9**) by reaction with EtOH–$HC(OEt)_3$ $MeSO_3H$ (95%). α-Deprotonation of **9** (LDA) and reaction with MeSSMe gave the ester **10**, R=Et, (100%), and this was cleaved to the acid **10**, R=H, using KOt-Bu–DMSO (87%). The ketone **1**, R=CH_2Ph, was obtained from this acid by oxidative decarboxylation[5] in 78% yield (93% corrected for recovered acid **10**). Baeyer-Villiger oxidation of **1**, R=CH_2Ph, basic hydrolysis of the resulting lactone and iodolactonation provided after recrystallization the iodo lactone **4**, in 83% yield overall from **1**, and 100% ee.[6]

The efficient process for the synthesis of chiral iodo lactone **4** coupled with the recently developed catalytic reduction of the keto lactone **11** to the 15-(*S*) alcohol,[7] i.e. the natural prostanoid configuration at C(15), provides a highly effective and flexible synthetic route to prostanoids which uses no chiral starting materials, but only readily available and recoverable chiral catalysts, which serve as molecular robots for synthetic purposes. Since the original synthesis of prostanoids[1] has been followed in many laboratories, the greatly improved version which is outlined herein is illustrated by the experimental procedures which follow.

(-)-3-(7'-Benzyloxymethyl-bicyclo[2.2.1]hept-5'-ene-2'-carbonyl)-1,3-oxazolin-2-one ((-)-8).[1,3] To a solution of 387 mg (0.75 mmol, 0.1 equiv) of ((-)-**5**[3]) in 7 ml of dry CH_2Cl_2 were added at -78 °C a solution of 1.06 g (7.5 mmol, 1 equiv) of **7** and dropwise at -78 °C a cold (-70 °C) solution of a freshly prepared diene (**6**) in 2 ml of CH_2Cl_2. After stirring for 18 h at -78 °C, the reaction solution was quenched at -78 °C with 2 ml of 1*N* aq. $NaHCO_3$ and with 2 ml of water, extracted with 50 ml of an additional CH_2Cl_2, washed with 10 ml of brine, and dried over $MgSO_4$. The crude product was chromatographed on silica gel (s.g.) with 1 : 2 EtOAc–hexane to afford 2.27 g (93% yield, 96% ee) of (-)-**8** as a yellow oil: $[\alpha]_D^{23}$ - 85.5°(*c* 0.96, $CHCl_3$). IR (neat): 1776 (COO), 1696 (CON) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.52 (1 H, dd, J= 4.5, 11.7 Hz), 1.94-2.11 (1 H, m), 2.16-2.29 (1 H, m), 2.91 (1 H, br), 3.24 (1 H, br), 3.36 (2 H, d, J= 7.3 Hz), 3.83-4.06 (3 H, m), 4.38 (2 H, t, J= 8.2 Hz), 4.43 (2 H, s), 5.70-5.80 (1 H, m), 6.04-6.15 (1 H, m), 7.18-7.39 (5 H, m).

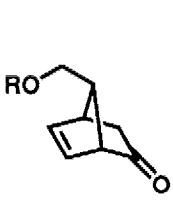
Ethyl 7-Benzyloxymethylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate (9). To a solution of 2.03 g (6.19 mmol, 1 equiv) of (-)-**8** in 124 ml of a 3 : 1 mixture of THF and water (0.05 M) were added at 0 °C 5.06 ml (49.5 mmol, 8 equiv) of 30% aq. H_2O_2 and 446 mg(18.6 mmol, 3 equiv) of lithium hydroxide.[4] After stirring for 23 h at 23 °C, 36.3 ml (54.5 mmol) of 1.5*N* aq. sodium sulfite was added at 0 °C to the suspension. The THF was removed and the aqueous solution was acidified at 0 °C, extracted with 4 : 1 ether–CH_2Cl_2. The dried extract was concentrated, dissolved in 1 : 1 EtOAc–hexane, filtered through s.g. and concentrated to give 1.60 g (100%) of carboxylic acid. This acid was stirred with 25 ml of 0.5M $MeSO_3H$ in absolute ethanol for 2 h at 23 °C and to the solution was added 2.01 ml (2 equiv) of triethyl orthoformate. The mixture was stirred for 37 h at 23 °C and evaporated. The residual oil was chromatographed on s.g. with 1 : 4 EtOAc–hexane to afford 1.65 g (95%) of (-)-**9** as a colorless oil.

7-Benzyloxymethyl-2-methylthiobicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (10, R=H). To a solution of 1.14 ml (8.12 mmol, 1.5 equiv) of diisopropylamine and 1.22 ml (8.12 mmol, 1.5 equiv) of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in 6 ml of anhydrous 1,2-dimethoxyethane (DME) was added at -78 °C 3.88 ml (7.41 mmol, 1.37 equiv) of 1.91M *n*-BuLi in hexane. After stirring for 75 min at 0 °C, a solution of 1.55 g (5.41 mmol, 1 equiv) of (-)-**9** in 3 ml of anhydrous DME was added dropwise at -78 °C. After stirring for 2 h at 0 °C, 0.73 ml (8.12 mmol, 1.5 equiv) of dimethyl disulfide was added dropwise at -78 °C to the enolate. The suspension was stirred for 1 h at -78 °C and for 6 h at 0 °C, quenched at 0 °C with 3 ml of sat. aq. NH_4Cl and with 15 ml of 2*N* aq. HCl, and evaporated. The aqueous solution was extracted with $CHCl_3$. Drying, concentration and s.g. chromatography with 1 : 2 EtOAc–hexane afforded 1.79 g (100%) of

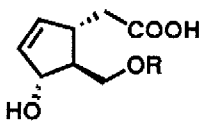
(-)-**10**, R=Et. To a solution of 1.69 g (5.10 mmol, 1 equiv) of this ester in 30 ml of dimethylsulfoxide was added 1.71 g (15.3 mmol, 3 equiv) of potassium *tert*-butoxide. After stirring for 4 h at 110 °C, the reaction mixture was acidified with 20 ml of 1*N* aq. HCl, stirred for 30 min at 23 °C, and extracted with 200 ml of EtOAc. After washing with brine and drying, the crude product was chromatographed on s.g. with 1 : 1 EtOAc–hexane to afford 1.35 g (87%) of acid **10**, R=H.

7-Benzyloxymethylbicyclo[2.2.1]hept-5-en-2-one (1, R=CH_2Ph). To a solution of 252 mg (0.832 mmol, 1 equiv) of **10**, R=H in 7 ml of 1% trimethyl orthoformate in anhydrous methanol was added 405 µl (0.832 mmol, 1 equiv) of 40% benzyltrimethylammonium methoxide in anhydrous methanol. After stirring for 3 h at 23 °C, a solution of 117 mg (0.874 mmol, 1.05 equiv) of *N*-chlorosuccinimide in 0.7 ml of anhydrous acetonitrile was added dropwise to the solution at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, quenched at 0 °C with 2 ml of 1*N* aq. HCl, and evaporated. The aqueous solution was dissolved in 4 ml of THF, stirred for 16 h at 23 °C, and evaporated and the residue was extracted with EtOAc. The ethyl acetate layers were combined and dried over $MgSO_4$. The crude product was chromatographed on silica gel with 1 : 4 EtOAc–hexane to afford 148 mg (78%) of **1**, R=CH_2Ph, as a colorless oil and 40.4 mg (16%) of recovered **10**, R=H, for **1**, R=CH_2Ph: $[\alpha]_D^{23}$ - 460°(*c* 2.28, $CHCl_3$). IR (neat): 1745 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (1 H, d, J= 16.5 Hz), 2.06 (1 H, dd, J= 3.0, 16.5 Hz), 2.74 (1 H, t, J= 7.1 Hz), 3.01 (1 H, br), 3.15 (1 H, br), 3.53 (2 H, d, J=7.1 Hz), 4.48 (2 H, s), 5.94 (1 H, dd, J= 2.4, 5.1 Hz), 6.40 (1 H, dd, J= 2.4, 5.1 Hz), 7.23 (5 H, m). The enantiomeric purity of ketone **1** is determined by HPLC analysis using a Daicel AD column with 1% isopropyl alcohol in hexane for elution.

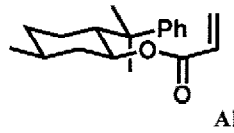
6-Benzyloxymethyl-7-hydroxy-8-iodo-2-oxabicyclo[3.3.0]octan-3-one (4). To a solution of 105 mg (0.461 mmol, 1 equiv) of **1**, R=CH_2Ph, in 5 ml of CH_2Cl_2 were added at 0 °C 95 mg (0.553 mmol, 1.2 equiv) of *m*-chloroperoxybenzoic acid (55%) and 105 mg (1.24 mmol, 2.7 equiv) of $NaHCO_3$. After stirring for 39 h at 0 °C, the mixture was quenched at 0 °C with 369 µl (0.553, 1.2 equiv) of 1.5*N* aq. Na_2SO_3, diluted with 1 ml of brine and extracted with CH_2Cl_2. After drying and removal of the solvent, 112 mg (100%) of Baeyer-Villiger lactone was obtained and this was dissolved in 800 µl of a 3 : 1 mixture of THF and methanol and treated with 277 ml (0.553 mmol, 1.2 equiv) of 2*N* aq. KOH. After stirring for 2 h at 23 °C, CO_2 was passed in and THF and methanol were removed. To the aqueous solution were added 55 mg (0.553 mmol, 1.2 equiv) of $KHCO_3$ and at 0 °C 234 mg (0.922 mmol, 2 equiv) of iodine, 168 mg (1.01 mmol, 2.2 equiv) of potassium iodide, 100 µl of THF, and 200 µl of CH_2Cl_2. The mixture was stirred at 24 h at 0 °C, decolorized at 0 °C with 256 mg (2.03 mmol, 4.4 equiv) of Na_2SO_3, and extracted with 4 : 1 EtOAc–CH_2Cl_2. The crude product was chromatographed on s.g. using 1 : 1 EtOAc–hexane. The organic layers were combined and dried over $MgSO_4$. The crude product was chromatographed on s.g. with 1 : 1 EtOAc–hexane to afford 160 mg (89%) of **4** as a pale yellow solid ($[\alpha]_D^{23}$ - 24.1°(*c* 1.38, $CHCl_3$)), which was recrystallized from CH_2Cl_2-ether-hexane to afford 150 mg (83% yield, 100% ee) of (-)-**4** as colorless prisms: m.p. 119-121°, $[\alpha]_D^{23}$ - 35.8°(*c* 1.1, $CHCl_3$), identical with an authentic sample.[1,2] The enantiomeric purity of iodolactone **4** was determined by HPLC analysis using a Daicel OD column with 20% isopropyl alcohol in haxane for elution.[8]



1

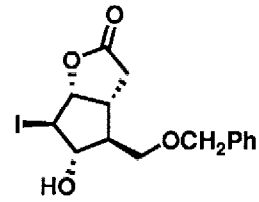


2

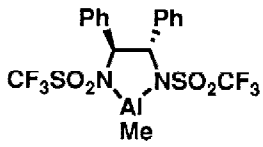


3

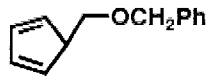
$AlCl_3$



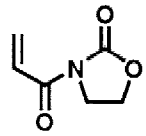
4



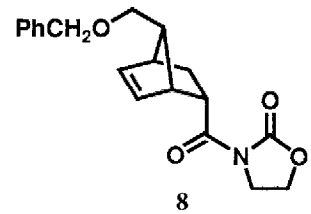
5



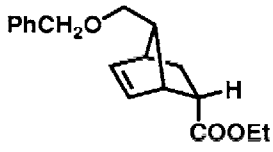
6



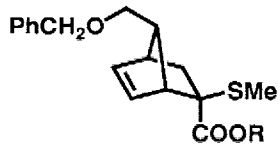
7



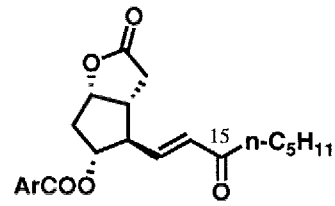
8



9



10



11

Reference and Notes

1. (a) Corey, E. J.; Weinschenker, N.M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677; (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinschenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397-398; (c) Corey, E. J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* **1971**, *93*, 4326-4327; (d) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley Inc. 1989; pp. 250-264.
2. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908-6909.
3. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.*. **1989**, *111*, 5493-5495. Very pure catalyst **5** can be obtained by recrystallization from CH_2Cl_2–heptane (dry). Using very pure **5** ee's as high as 98% have been obtained for **8**.
4. Evans, D. A.; Britton, T. C.; Ellman, J. A.; *Tetrahedron Lett.* **1987**, *28*, 6141-6144.
5. (a) van Tamelen, E. E.; Haarstad, V. B.; Orvis, R. L.; *Tetrahedron Lett.*, **1968**, *24*, 687-704; (b) Trost, B. M.; Tamaru, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3101-3113.; **1975**, *97*, 3528-3530.
6. We have also succeeded in the conversion ester **9** to **1**, R=CH_2Ph, using the α-hydroxylation methodology of Wasserman, H. H.; Lipschutz, B. H. *Tetrahedron Lett.* **1975**, 1731-1734.
7. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.
8. This research was assisted by grants from the National Institutes of Health and the National Science Foundation.

(Received in USA 13 March 1991; accepted 16 October 1991)