Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 8, pp. 2053-2058, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00267-7

Preparation of Chiral Building Blocks for Synthesis of *Aconitium* Alkaloids

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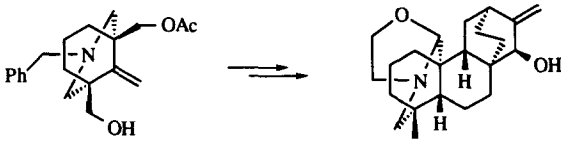
Abstract: Treatment of *meso*-diols **3** and **6** with CCL and vinyl acetate without solvent produced the AE part of *Aconitium* alkaloids **2** and **7** in 68% and 75% yields, respectively, with > 96% e.e. Quantitative formations of their MTPA esters **4** and **8** were achieved by reaction with MTPA in the presence of DCC and DMAP in $ClCH_2CH_2Cl$.

Introduction

Recently, we reported the first asymmetric total synthesis of atisine (**1**) *via* an intramolecular double Michael reaction.[1] Although the chiral precursor **2** was synthesized in a highly enantioselective manner by the application of lipase catalyzed irreversible transesterification,[2] the isolated yield was poor.[1] Since **2** would be a common building block of *Aconitium* alkaloids as the AE part[3] and a useful intermediate in terpene syntheses, the asymmetric synthesis of **2** has been further investigated. Here, we describe a more efficient production of **2** and the result of the transesterification of a carbamate **6**.

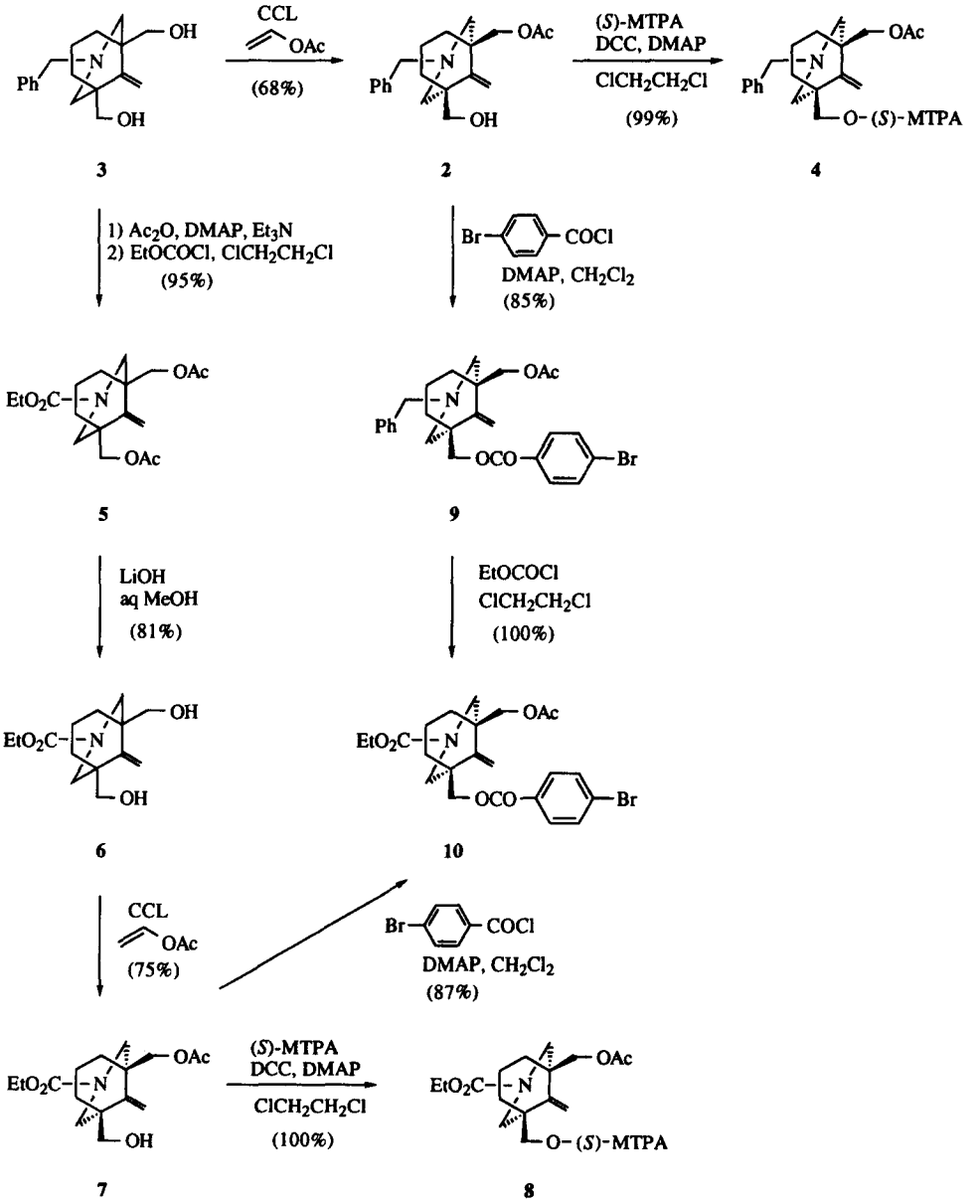


2 **1**

Results and Discussion

Treatment of **3** with *Candida cylindracea* lipase (CCL) and vinyl acetate in benzene had provided the enantiomerically pure **2** in 32% yield together with the starting **3** (66% yield) and its diacetate (1% yield).[1] Wang and coworkers recorded the rate of transesterification was slow in more polar solvents than in less polar solvents.[2] After a number of trials in various organic solvents, we found the reaction proceeded without solvent in a reasonable rate with a high enantioselectivity. Namely, reaction of **3** with CCL and vinyl acetate for 16 h at ambient temperature gave **2**, $[\alpha]_D^{20}$ –4.99 (MeOH) [lit.,[1] $[\alpha]_D^{28}$ –5.10 (MeOH)], in 67.8% yield along with **3** (23.3% yield) and its diacetate (6.9%). It was obsereved that the yield of **2** would be increased by the use of larger amount of CCL and the longer reaction time. After conversion into the (*S*)-MTPA eater **4**, the

enantiomeric purity of **2** was determined as > 96% e.e. Formation of the MTPA ester **4** upon the treatment with MTPA[4] in the presence of DCC and DMAP[5] in CH_2Cl_2 was sluggish. We observed the reaction was greatly accelerated by the use of $ClCH_2CH_2Cl$ as solvent. Namely, treatment of **2** with a small excess of MTPA in the presence of DCC and DMAP in $ClCH_2CH_2Cl$ for 1 h at ambient temperature afforded **4** quantitatively.



We were interested in the study on the necessity of the amine function for the enantioselective transformation of the *meso*-compound into the chiral one. Therefore, the conversion of the *N*-benzyl compound **3** into the carbamate **6** was examined. Direct conversion of **3** into **6** gave unsatisfactory results. Carbamate formation was carried out effectively, after conversion into its diacetate, by the treatment with ethyl chloroformate in hot $ClCH_2CH_2Cl$. Thus, **6** was synthesized from **3** in three steps. The diol **6**, mp 151–152 °C, was scarcely soluble in organic solvents. The transesterification using CCL and vinyl acetate in organic solvent such as benzene or MeCN resulted in failure. On the other hand, reaction of **6** with CCL and vinyl acetate without solvent provided **7**, $[\alpha]_D^{22}$ –8.77 ($CHCl_3$), in 75.0% yield together with **6** (21.0% yield) and **5** (3.8%). ^{1}H-NMR spectral (500 MHz) comparison of (*S*)-MTPA ester **8** of the optically active **7** with that derived from the racemate, which were prepared under the same reaction conditions as above, indicated > 96% e.e. of **7**.

The absolute configuration of **6** was determined by the correlation with **2** as follows. After conversion of **2** into *p*-bromobenzoate **9**, its treatment with ethyl chloroformate in hot $ClCH_2CH_2Cl$ provided quantitatively **10**, $[\alpha]_D^{20}$ +4.06 (MeOH). *p*-Bromobenzoylation of **7** gave **10**, $[\alpha]_D^{21}$ +4.04 (MeOH). It has been thus established that the product **7** has the (1*R*, 5*S*) configuration.

Summary

The enantioselective transesterifications of **3** and **6** were efficiently performed by treatments with vinyl acetate and CCL without solvent. The presence of tertiary amine function and benzyl group are not essential for the enantioselective transformation; this fact would indicate that the enzyme recognizes global molecular structure. Furthermore, it was found that $ClCH_2CH_2Cl$ is a good choice as a solvent for MTPA ester formation using MTPA in the presence of DCC and DMAP.

Experimental Section

General Remarks.

^{1}H-NMR spectra were taken on JOEL GX-500 using TMS as internal standard. Mass spectra were recorded on JEOL-DX-300 and JEOL-JMS-DX-303 instruments. Optical rotations were measured by HORIBA SEPA-300 polarimeter.

All reactions were carried out under a positive atmosphere of dry Ar. Solvents were distilled prior to use: CH_2Cl_2 and $ClCH_2CH_2Cl$ were distilled from CaH_2 and kept over 4-Å molecular sieves. All reaction extracts were dried over $MgSO_4$ and the solvent was removed by rotary evaporation under reduced pressure. Flash chromatography was performed using Merck Kieselgel 60 Art. 9835. CCL Type VII (SIGMA) was used.

(-)-(1*R*,5*S*)-1-(Acetoxymethyl)-3-benzyl-5-hydroxymethyl-9-methylene-3-azabicyclo-[3.3.1]nonane (2).

A mixture of **3**[1] (100 mg, 0.35 mmol) and CCL (100 mg) in vinyl acetate (3 ml) was stirred for 16 h at ambient temperature under protection from light. After dilution with benzene, the mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$, H_2O and brine, dried and evaporated. The residue was

subjected to flash chromatography with hexane-AcOEt (9 : 1 v/v) as eluent to afford the corresponding diacetate (8.9 mg, 6.9%) and **2** (77.7 mg, 67.8%) as an oil: $[\alpha]_D^{20}$ –4.99 (c 2.6, MeOH) [lit.,[1] $[\alpha]_D^{28}$ –5.10 (c 0.96, MeOH)], whose spectral data were identical with those of the authentic compound.[1] Further elution with benzene-acetone (4 : 1 v/v) yielded **3** (23.3 mg, 23.3%).

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To a stirred solution of **2** (15.8 mg, 0.048 mmol), (*S*)-MTPA (13.5 mg, 0.057 mmol) and DMAP (1.0 mg, 0.008 mmol) in $ClCH_2CH_2Cl$ (1 ml) was added a solution of DCC (11.9 mg, 0.057 mmol) in $ClCH_2CH_2Cl$ (1 ml) under cooling with ice. After 1 h of stirring at ambient temperature, followed by dilution with hexane-Et_2O (1 : 1 v/v), the mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ and brine, dried and evaporated. Flash chromatography of the crude product with hexane-AcOEt (5 : 1 v/v) as eluent afforded **4** (25.2 mg, 99%) as an oil, whose ^{1}H-NMR spectrum (500 MHz, $CDCl_3$) was identical with that of the authentic compound.[1]

1,5-(Diacetoxymethyl)-3-ethoxycarbonyl-9-methylene-3-azabicyclo[3.3.1]nonane (5).

A mixture of the diacetate[1] (140 mg, 0.37 mmol), prepared from **3**, and ethyl chloroformate (0.6 ml, 6.3 mmol) in $ClCH_2CH_2Cl$ (5 ml) was heated for 8 h under reflux. After dilution with benzene-Et_2O (1 : 1 v/v), the mixture was washed with 8% $KHSO_4$, saturated $NaHCO_3$ and brine, dried and evaporated. The residue was purified by flash chromatography with hexane-AcOEt (85 : 15 v/v) to provide **5** (126.5 mg, 95%) as an oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.3 Hz), 1.45–1.60 (3H, m), 1.90–2.09 (3H, m), 2.10 (6H, s), 2.75–2.85 (2H, m), 4.06 and 4.09 (each 2H, each d, each J = 11.6 Hz), 4.15–4.39 (4H, m), 4.73 (2H, br s); mass spectrum *m/z* 353 (M^+). Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.53; H, 7.60; N, 4.10.

3-Ethoxycarbonyl-1,5-(dihydroxymethyl)-9-methylene-3-azabicyclo[3.3.1]nonane (6).

A mixture of **5** (232 mg, 0.66 mmol), $LiOH{\cdot}H_2O$ (82 mg, 1.97 mmol) and H_2O (2 ml) in MeOH (6 ml) was stirred for 3 h at ambient temperature. After concentration under reduce pressure, followed by acidification with 10% HCl, the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to give a residue, which was subjected to flash chromatography. Elution with hexane-AcOEt (1 : 1 v/v) afforded **6** (142 mg, 81%) as scales: mp 151–152 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.3 Hz), 1.42–1.63 (5H, m), 1.92–2.08 (3H, m), 2.86–2.92 (2H, m), 3.60–3.75 (4H, m), 4.18–4.30 (4H, m), 4.79 (1H, br s), 4.85 (1H, br s); mass spectrum, *m/z* 270 (M^+ +1). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.40; H, 8.54; N, 5.24.

(-)-(1*R*,5*S*)-1-(Acetoxymethyl)-3-ethoxycarbonyl-5-hydroxymethyl-9-methylene-3-azabicyclo[3.3.1]nonane (7).

A mixture of **6** (50 mg, 0.18 mmol) and CCL (50 mg) in vinyl acetate (6 ml) was stirred for 2 days at ambient temperature under protection from light. After addition of CCL (50 mg), the mixture was further stirred for 1 day under the same conditions. After filtration through Celite, the filtrate was washed with saturated $NaHCO_3$, H_2O, and brine, dried, and evaporated. Flash chromatography of the residue with benzene-acetone (9 : 1 v/v) as eluent gave the diacetate **5** (2.5 mg, 3.8%) and **7** (43.5 mg, 75.0%) as an oil: $[\alpha]_D^{22}$ –8.77 (c 2.0, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$); δ 1.28 (3H, t, J = 7.3 Hz), 1.42–1.64 (4H, m), 1.92–2.08 (3H,

m), 2.09 (3H, br s), 2.75–2.92 (2H, m), 3.61 and 3.70 (each 1H, each d, each J = 11 Hz) 4.07 (2H, s), 4.10–4.37 (4H, m), 4.72 and 4.76 (each 1H, each br s); mass spectrum, *m/z* 312 (M^+ +1); exact mass calcd for $C_{16}H_{26}NO_5$ 312.1833 (M^+ +H), found 312.1811. Further elution with benzene-acetone (4 : 1 v/v) yielded **6** (10.6 mg, 21.0%).

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To a stirred solution of **7** (14.4 mg, 0.046 mmol), (*S*)-MTPA (21.6 mg, 0.092 mmol) and DMAP (2.0 mg, 0.016 mmol) in $ClCH_2CH_2Cl$ (2 ml) was added slowly a solution of DCC (19.0 mg, 0.092 mmol) in $ClCH_2CH_2Cl$ (1 ml) under cooling with ice. After being stirred for 3 h at ambient temperature, the work up and purification of the product as the case of the preparation of **4** gave **8** (24.4 mg, 100%) as an oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.22–1.28 (3H, m), 1.42–1.60 (3H, m), 1.90–2.08 (3H, m), 2.09 (3H, s), 2.72–2.83 (2H, m), 3.54 (3H, s), 4.06–4.40 (8H, m), 4.65 and 4.71 (each 1H, each br s), 7.42–7.51 (5H, m); mass spectrum, *m/z* 527 (M^+); exact mass calcd for $C_{26}H_{32}NO_7F_3$ 527.2129 (M^+), found 527.2130.

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(±)-**7** (11.0 mg, 0.35 mmol) was similarly converted into the MTPA ester (18.2 g, 98%) as an oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.21–1.29 (3H, m), 1.42–1.60 (3H, m), 1.85–2.08 (3H, m), 2.09 (3H, s), 2.72–2.85 (2H, m), 3.54 and 3.55 (each 1.5H, each s), 4.06–4.40 (8H, m), 4.65 and 4.71 (each 1H, each br s), 7.42–7.51 (5H, m).

(+)-(1*R*,5*S*)-1-(Acetoxymethyl)-3-benzyl-5-(*p*-bromobenzoyloxymethyl)-9-methylene-3-azabicyclo[3.3.1]nonane (9).

To a stirred solution of **2** (90 mg, 0.27 mmol) and DMAP (100 mg, 0.82 mmol) in CH_2Cl_2 (3 ml) was added a solution of *p*-bromobenzoyl chloride (179 mg, 0.82 mmol) in CH_2Cl_2 (3 ml) under cooling with ice. After being stirred for 1 h at ambient temperature, followed by dilution with benzene-Et_2O (1 : 1 v/v), the mixture was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was subjected to flash chromatography with hexane-AcOEt (9 : 1 v/v) to provide **9** (118.4 mg, 85%) as an oil: $[\alpha]_D^{23}$ +2.98 (c 3.5, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.46–1.61 (2H, m), 1.94–2.09 (4H, m), 2.05 (3H, s), 3.01 and 3.03 (each 2H, each d, each J = 6.8 Hz), 3.35 and 3.50 (each 1H, each d, each J = 13.0 Hz), 4.05 (2H, s), 4.21 and 4.27 (each 1H, each d, each J = 10.8 Hz), 4.68 and 4.71 (each 1H, each br s), 7.27–7.34 (5H, m), 7.55 and 7.77 (each 2H, each d, each J = 8.5 Hz); mass spectrum, *m/z* 511 and 513 (M^+). Anal. Calcd for $C_{27}H_{30}BrNO_4$: C, 63.28; H, 5.90; N, 2.73. Found: C, 63.07; H, 5.97; N, 2.53.

(+)-(1*R*,5*S*)-1-(Acetoxymethyl)-5-(*p*-bromobenzoyloxymethyl)-3-ethoxycarbonyl-9-methylene-3-azabicyclo[3.3.1]nonane (10).

(A) By the same means for the preparation of **9**, **7** (50 mg, 0.16 mmol) was transformed into **10** (69.2 mg, 87%) as an oil: $[\alpha]_D^{21}$ +4.04 (c 5.7, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 6.1 Hz), 1.30–1.64 (3H, m), 1.97–2.09 (3H, m), 2.11 (3H, br s), 2.74–2.96 (2H, m), 4.11–4.50 (8H, m), 4.78 and 4.83 (each 1H, each br s), 7.59–7.62 (2H, m), 7.89–7.91 (2H, m); mass spectrum, *m/z* 493 and 495 (M^+). Anal. Calcd for $C_{23}H_{28}BrNO_6$: C, 55.87; H, 5.71; N, 2.83. Found: C, 55.69; H, 5.84; N, 2.70.

(B) A mixture of **9** (80 mg, 0.16 mmol) and ethyl chloroformate (0.5 ml, 5.26 mmol) in $ClCH_2CH_2Cl$ (5 ml) was heated for 8 h under reflux. After dilution with benzene, the mixture was washed with 8% $KHSO_4$,

saturated $NaHCO_3$ and brine, dried, and evaporated. Flash chromatography of the crude product with hexane-AcOEt (9 : 1 v/v) gave **10** (77.0 mg, 100%) as an oil, ^{1}H-NMR spectrum of which was identical with that of the sample prepared by the method A: $[\alpha]_D^{20}$ +4.06 (c 7.3, MeOH).

Acknowledgment

We thank to Mr. K. Kawamura, Mrs. M. Suzuki, Mrs. A. Satoh, and Miss Y. Maehashi, Pharmaceutical Institute, Tohoku University, for microanalysis, spectral measurements, and the preparation of the manuscript. This work was, in part, supported by Mitsumaru Pharmaceutical Co., LTD, which is greatly acknowledged.

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(*Received in Japan* 26 *June* 1995)