室蘭工業大学
学術資源アーカイブ
Muroran Institute of Technology Academic Resources Archive

Investigations Directed Toward the Synthesis of New Cyclopentanoids Using Optically Active Bicyclo[2.2.1]heptene Monoester

Investigations Directed Toward the Synthesis of New Cyclopentanoids Using Optically Active Bicyclo[2.2.1]heptene Monoester

Satomi Niwayama*[1,2]

[1]Graduate School of Engineering, Muroran Institute of Technology, 27-1, Mizumoto-cho, Muroran, Hokkaido, 050-8585, Japan
[2]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku, Tokyo, 113-0033, Japan

---

Abstract : *The synthetic utilization of a chiral building block obtained by the enzymatic asymmetric hydrolysis of a symmetric diester having the bicyclo[2.2.1]heptene system was investigated. Several cyclopentanoids have been synthesized in high yields in enatiomerically enriched forms with the use of simple reactions. These compounds are expected to serve as useful chiral synthons for cyclopentane-containing natural products and pharmaceuticals.*

Keywords : *chiral synthon, cyclopentanoids, enzymatic reaction, natural products, pharmaceuticals*

I. Introduction

Development of efficient methodologies for controlling stereogenic centers has been the central issue for the synthesis of natural products and pharmaceuticals. For production of enantiomerically enriched compounds, several methods are possible, such as utilization of chiral auxiliaries and asymmetric reactions. Among these methods, an enzymatic asymmetric reaction is one of the most powerful tools for performing these syntheses. Although the drawback is that the mechanisms are not fully understood and therefore random screening of the enzymes and the substrates often becomes mandatory, the reaction conditions are mild, simple, and environmentally benign. Therefore, a number of synthons produced by enzymatic reactions have been applied to synthesis of important classes of pharmaceuticals and bioactive natural products. For example, Ohno et al. reported synthesis of various nucleosides and carbapenems [1-4]. Nagao et al. reported synthesis of (+)-carbacyclin [5], and Yu et al. reported the paroxetine [6]. All of these compounds are known to exhibit important therapeutic properties. More recently, Back and Materson et al. reported amino acid derivatives from chiral monoesters obtained by enzymatic reactions [7-8].

Here we wish to report our approach for synthesis of some cyclopentanoids initiated by an enzymatic reaction. The cyclopentane ring and its derivatives are found in a number of significant pharmaceuticals and natural products, such as prostanoids and carbocyclic nucleosides as well as in their related compounds, and therefore such compounds are anticipated to be useful synthons for synthesis of these derivatives.

II. Results and Discussion

The symmetric bicyclo[2.2.1]heptene diester, **1**, was monohydrolyzed with an enzyme, pig liver esterase, yielding the corresponding monoester, **2**, according to the procedures Ohno et al. reported [1] (Scheme 1). This monoester, **2**, was previously applied to the synthesis of carbocyclic nucleosides via the regiospecific decarboxylative ozonolysis of the double bond as noted above [1]. Here, a more challenging stereo-differentiation was attempted by the cleaving of the C_5-C_6 bond, which is more remote from the two different substituents.

The monoester, **2**, possesses a characteristically long conjugated system in that it has a carboxyl group and a carbomethoxy group. Although some attempts to modify only one of these functional groups were made, such as Arndt- Eistert homologation of the carboxyl group and selective reduction of one of the substituents, none was successful for this monoester. However, hydrogenation of the C=C bond afforded **3** in quantitative yield, in which the two functional groups are closer to the C_5-C_6 bond (Scheme 2). Although selective reduction of one of the substituents was still difficult at this stage due to the proximity of the two groups, diborane reduction of the carboxyl group in dilute THF solution followed by catalytic acid treatment afforded the lactone **4** in 85% yield as a white solid. The deprotection of the acetonide group of **4** unexpectedly required harsh conditions. After several attempts at acid hydrolysis, refluxing **4** with the ion exchange resin Dowex 50W in water for two days turned out to be the only effective method, affording the diol, **5**, in about 90% yield.


At this stage, the oxidative cleavage of the C_5-C_6 bond followed by regioselective modification to the resultant dialdehyde was extensively studied. In the end, diol **5** was submitted to oxidative cleavage with $Pb(OAc)_4$ in benzene containing 30% methanol. The resultant dialdehyde was obtained as the hemiacetal, **6**, in which the methoxy group was introduced exclusively from the carbonyl side. Since the acetal, **6**, is unstable, this acetal was immediately subjected to oxidation with PCC to afford a white crystalline solid, **7**, in a reasonably high yield from the diol (73%, 2 steps). This regioselective introduction of the methoxyl group is explained by the participation of the carbonyl group of the lactone ring (Scheme 2).

The white solid, **7**, is stable and can be a versatile potential intermediate for further stereoselective and stereospecific modification. For example, selective methylation on the acetal carbon was possible under several conditions, although the conditions have not been optimized at this point.

In another attempt, dimethylation of the dialdehyde derived from oxidative cleavage of diol **5** was carried out to yield a diastereomeric mixture of diol **8**. This stable diol also appears to be a potential precursor of cyclopentanoids, and it appears to be capable of selective monoprotection due to the steric hindrance by the carbonyl group of the lactone. In fact, on a small scale, it underwent selctive monobenzylation (Ag_2O/BnBr, Et_2O reflux) yielding the monoprotected alcohol, and subsequent oxidation with PCC (PCC/3A molecular sieves, CH_2Cl_2) afforded the monomethyl ketone.

III.   Schemes

Scheme 1
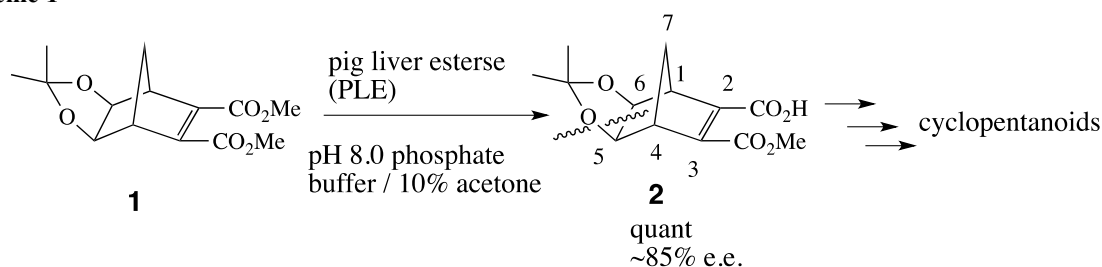
Scheme 2
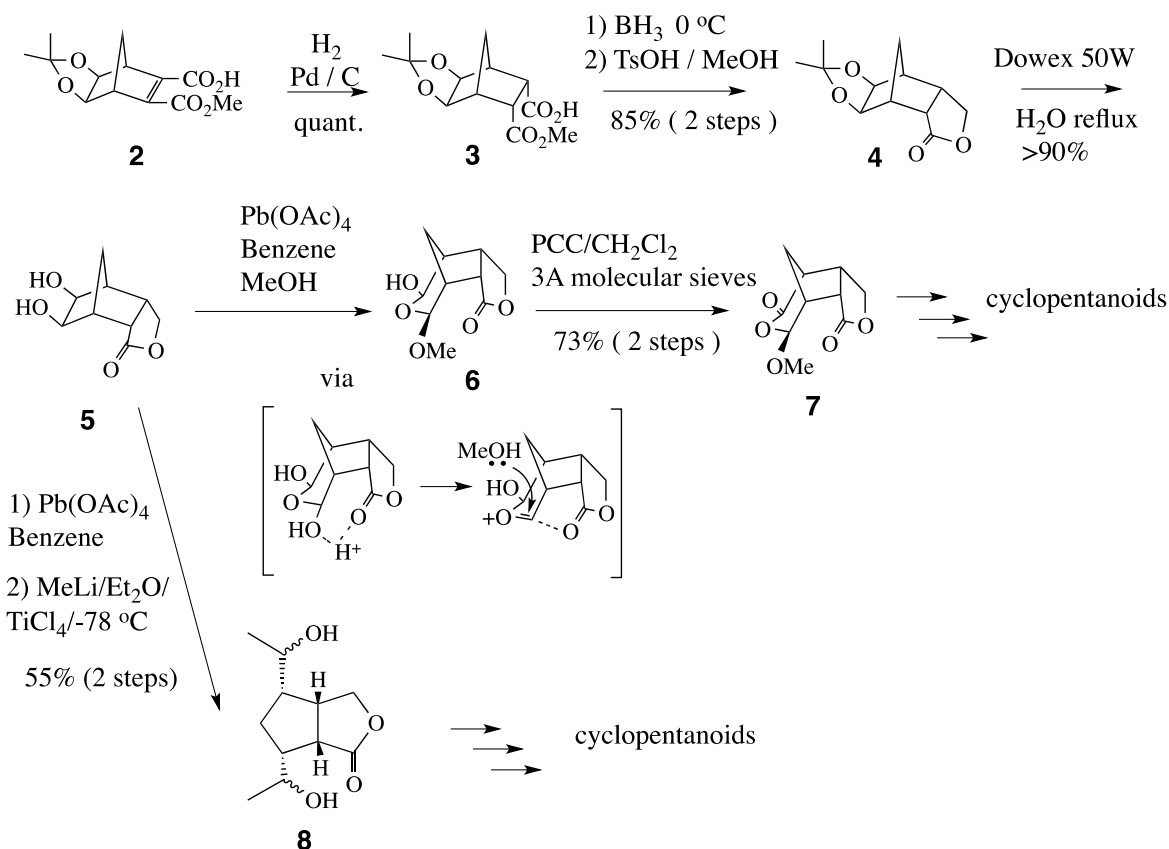
IV. Conclusion

In summary, synthetic development of chiral bicyclo[2.2.1]cycloheptene monoester, **2**, has been studied for the syntheses of several cyclopentanoids. This monoester, **2**, and the antipodal monoester **2'** were also synthesized non-enzymatically from D-mannitol by Ortuño et al. [9] and from a chiral sulfoxide by Carretero et al. [10], and some potential or true precursors for antibiotics were prepared from them [9]. They are applied to synthesis of precursors of carbocyclic nucleosides and relevant compounds. Therefore, the synthetic versatility of this chiral building block, **2**, is also anticipated [11].

V. Experimental

Representative experimental procedures are as follows:

Compound 3:

Monoester **2** (4.537 g, 16.9 mmol) was dissolved in MeOH 50 mL, and 10% Pd-C (700 mg) was added under an argon atmosphere. After replacing the argon with hydrogen, the mixture was stirred under a hydrogen atmosphere at room temperature overnight. The mixture was filtered through celite, and evaporation under reduced pressure afforded a white solid, **3**. Yield: 4.684 g (100%)

^{1}H-NMR (100MHz, CDCl$_3$) δ(ppm): 8.9 (1H, br.), 4.60 (2H, br. s), 3.68 (3H, s), 3.30 (2H, m), 2.65 (2H, br. s), 1.95 (1H, br. d, J=11.4), 1.45 (3H, s), 1.29 (3H, s), 1.15 (1H, br. d, J=11.4); IR (CHCl$_3$): 2500-3100, 1740, 1720, 1200, 1140; m.p.:149.5-150.5 ^{o}C (from hexane-EtOH); [α]$_D^{23}$: -4.42^o(c=1.2 in CHCl$_3$); MS: 270 (M$^+$), 255 (M$^+$-CH$_3$)

Compound 4:

Compound **3** (2.644 mg, 9.79 mmol) was dissolved in freshly distilled THF (150 mL) and 9 mL of BH$_3$/THF solution (2.43 mmol/mL) was added dropwise under an argon atmosphere at -5 ^{o}C ~ -10 ^{o}C. The mixture was stirred at room temperature for 2 days, and water was added dropwise at 0 ^{o}C until gas evolution stops. After a small amount of MeOH was added, the volume of the mixture was concentrated under reduced pressure to about 1/10, the product was extracted with CH$_2$Cl$_2$, and the organic layer was dried over anhydrous Na$_2$SO$_4$. After the organic solvent was evaporated under reduced pressure, the residue was dissolved in MeOH 1.5 mL and p-toluenesufonic acid (900 mg) was added. After stirring for 3 days at room temperature, CH$_2$Cl$_2$ (100 mL) was added to the mixture, washed with saturated sodium bicarbonate solution, brine, and dried over anhydrous Na$_2$SO$_4$, and purified by column chromatography to afford white crystal, **4**. Yield: 1.858 g (85%)

^{1}H-NMR (400MHz, CDCl$_3$) δ (ppm): 4.35-4.25 (4H, m), 3.06 (1H, m), 2.90 (1H, m), 2.76 (1H, m), 2.44 (1H, m), 2.00 (1H, br. d, J=12.0), 1.48 (3H, s), 1.35 (1H, br. d, J=12.0), 1.30 (3H, s); ^{13}C-NMR (25MHz, CDCl$_3$) δ (ppm): 189.04, 109.04, 78.64, 77.04, 67.84, 43.84, 43.52, 43.28, 38.64, 35.44, 25.44, 24.16; IR (CHCl$_3$): 1760, 1260, 1100-1000; m.p.:129.5-130.5 ^{o}C (from hexane-CH$_2$Cl$_2$); [α]$_D^{23}$: -112.8^o (c=0.135 in CHCl$_3$); Anal. Calc. for C$_{12}$H$_{16}$O$_4$ C: 64.27 H: 7.19, found C: 64.06, H: 7.15

Compound 5:

To compound **4** (132 mg, 0.59 mmol) was added H$_2$O (30 mL) and resin (Dowex 50W)(130 mg), and the mixture was refluxed for 2 days. After cooling to r.t., the mixture was filtered through filtering paper and evaporated with a small amount of MeOH under reduced pressure to afford a white solid, **5**, which was used without purification for further steps.

Yield: 108 mg (99%)

^{1}H-NMR (90 MHz, CDCl$_3$/CD$_3$OD) δ(ppm): 4.3 (2H, m), 3.9 (2H, m), 3.4 (1H, m), 3.0(1H, m), 2.6 (1H, m), 2.3 (1H, m), 2.10 (1H, br. d, J=10.5), 1.43 (1H, br. d, J=10.5); IR (CHCl$_3$): 3400-3500, 1760, 1260

Compound 7:

Compound **5** (206 mmg, 1.120 mmol) was stirred with 90% Pb(OAC)$_4$ (650 mg, 1.319 mmol) in benzene 9 mL and MeOH 2 mL at r.t. for 5h under an argon atmosphere. After 30 mL of ether was added, the mixture was filtered through celite, and concentrated under reduced pressure. At this point, the structure of the residue was confirmed as compound **6**. Then it was stirred overnight with PCC (375 mg, 1.74 mmol) and activated 3A molecular sieves in CH$_2$Cl$_2$ under an argon atmosphere at r.t. The mixture was passed through a Florisil/ether short column and purified by column chromatography to afford a white solid, **7**. Yield: 165 mg (73%, 2 steps)

^{1}H-NMR (400MHz, CDCl$_3$) δ (ppm): 5.12 (1H, d, J=2.6), 4.82 (1H, dd, J=1.8, 10.3), 4.40 (1H, dd, J=10.3, 5.9), 3.49 (3H, s), 3.35 (2H, m), 3.16 (1H, m), 2.99 (1H, m), 2.43 (1H, m), 2.26 (1H, m); ^{13}C -NMR (25MHz, CDCl$_3$) δ (ppm): 178.56, 175.58, 109.44, 67.49, 57.31, 49.06, 46.56, 46.08, 43.68 31.68; IR (CHCl$_3$): 1775;

m.p.:137.0-138.0 ^{o}C (from hexane-CH$_2$Cl$_2$); [α]D^{21}: -3.45^o(c=0.6 in CHCl$_3$); Anal. Calc. for C$_{10}$H$_{12}$O$_5$ C: 56.60 H: 5.70, found C: 56.87, H: 5.71

Compound 8:

Compound **5** (398 mmg, 2.166 mmol) was stirred with 90% Pb(OAC)$_4$ (1.173 g, 2.383 mmol) in benzene 17 mL for 5h at r.t. under an argon atmosphere. After 35 mL of ether was added, the mixture was filtered through celite, and concentrated under reduced pressure. This mixture in CH$_2$Cl$_2$ (2 mL) was added dropwise to another flask containing 1.25 M MeLi (26.3 mL, 32.9 mmol) and TiCl$_4$ (6.26 g, 32.9 mmol) in freshly distilled ether (35 mL) at -78 ^{o}C under argon atmosphere. The reaction mixture was worked up by ice-salt water, extracted with ethyl acetate, and dried over anhydrous Na$_2$SO$_4$. After the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography to afford compound **8**. Yield: 257 mg (55%)

^{1}H-NMR (100MHz, CDCl$_3$) δ (ppm): 4.2-4.4 (2H, m), 3.6-3.8 (2H,m), 3.1-3.3 (1H, m), 2.8-3.1 (1H, m), 1.8-2.2 (4H, m), 1.6-1.8 (2H, m), 1.1-1.3 (6H, m); IR (CHCl$_3$): 3400, 1750, 1100; MS: 214 (M$^+$), 196 (M$^+$-H$_2$O), 178 (M$^+$-2H$_2$O)

References and Notes

[1]. M. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, *J. Am. Chem. Soc.*, 1983, **105**, 4049.
[2]. M. Ohno, Y. Ito, M. Arita, T. Shibata, K. Adachi, and H. Sawai, *Tetrahedron*, 1984, **40**, 145.
[3]. K. Okano, T. Izawa and M. Ohno, *Tetrahedron Lett.*, 1983, **24**, 217
[4]. T. Iimori, Y. Takahashi, T. Izawa, S. Kobayashi and M. Ohno, *J. Am. Chem. Soc.*, 1983, **105**, 1659.
[5]. S. Sano, H. Ushirogochi, K. Morimoto, S. Tamai, and Y. Nagao, *Chem. Commun*., 1996, 1775.
[6]. M. S. Yu, I. Lantos, Z.-Q. Peng, J. Yu, and T. Cacchio, *Tetrahedron Lett*., 2000, **41**, 5647.
[7]. V. Iosub, A. R. Haberi, J. Leung, M. Tang, K. Vembaiyan, M. Parez, and T. G. Back, *J. Org. Chem.,* 2010, **75**, 1612.
[8]. S. Baberjee, W. J. Wiggins, J. L. Geoghegan, C. T. Anthony, E. A. Woltering, and D. S. Masterson, *Org. Biomol. Chem*., 2013, **11**, 6307.
[9]. M. Díaz, J. Ibarzo, J. M. Jiménez, and R. M. Ortuño, *Tetrahedron Asymmetry*, 1994, **5**, 129
[10]. I. Alonso, M. B. Cid, J. C. Carretero, J. L. García-Ruano, and M. A. Hoyos, *Tetrahedron Asymmetry*, 1991, **2**, 1193.
[11]. Synthesis of racemic **2** is also reported. S. Niwayama, *J. Org. Chem*. 2000, **65**, 5834.