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Enantioselective Deprotonation of *meso*-Cycloheptanone Derivative: Application to the Synthesis of a Potential Intermediate for Pseudomonic Acid B

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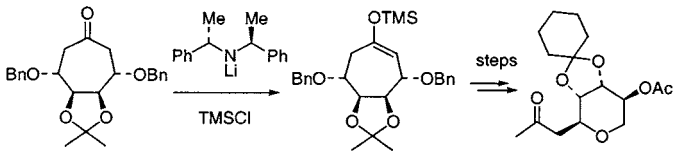
ABSTRACT



A novel synthetic path to a potential intermediate for the synthesis of pseudomonic acid B was established by employing enantioselective deprotonation of a *meso*-cycloheptanone derivative bearing hydroxy groups at the 3,4,5,6-positions with lithium (*S*,*S*′)-α,α′-dimethyldibenzylamide as a key step.

The enantioselective deprotonation strategy has been recognized as a powerful synthetic tool for introducing a chiral center to meso or prochiral compounds.[1] This methodology has often been applied to five- or six-membered cycloalkanones generating the desired chirality with high enantiomeric excess, aimed at the synthesis of biologically active compounds, including natural products. However, little attention has been paid to the introduction of chirality into simple seven-membered cycloalkanones by application of this strategy, probably due to their conformational flexibility. Therefore, it is very interesting to investigate a further applicability of the enantioselective deprotonation strategy to cycloheptanone derivatives to develop its usefulness.[2]

Recently, we have been involved in the synthesis of biologically active compounds using an enantioselective deprotonation strategy.[3] In connection with our continuous interest in developing synthetic methods through the use of enantioselective deprotonation reaction, we are interested in a chiral synthesis of a potential intermediate for pseudomonic acid B starting from a *meso*-cycloheptanone derivative, where

(1) (a) Koga, K. *J. Synth. Org. Chem., Jpn.* **1990**, *48*, 463. (b) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487. (c) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 1021. (d) Simpkins, N. S. *Chem. Soc. Rev.* **1990**, *19*, 335. (e) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. (f) Simpkins, N. S. *Pure Appl. Chem.* **1996**, *68*, 691. (g) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. (h) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (i) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 95.

(2) To the best of our knowledge, no report for an enantioselective deprotonation of simple cycloheptanone derivatives has been published. For cyclooctanone derivatives; see: (a) Berkowitz, W. F.; Wu, Y. *J. Org. Chem.* **1997**, *62*, 1536. (b) Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1985. (c) Gambacorta, A.; Tofani, D.; Lupattelli, P.; Tafi, A. *Tetrahedron Lett.* **2002**, *43*, 2195. For bicyclo[3.2.1]octanone system; see: (d) Cox, P. J.; Simpkins, N. S. *Synlett* **1991**, 321. (e) Majewski, M.; Zheng, G.-Z. *Synlett* **1991**, 173. (f) Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3113. (g) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533. (h) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207. (i) Majewski, M.; Lazny, R. *Tetrahedron Lett.* **1994**, *35*, 3653. (j) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825. (k) Coggins, P.; Gaur, S.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, *36*, 1545. (l) MaGee, D. I.; Setiadji, S.; Martin, R. A. *Tetrahedron: Asymmetry* **1995**, *6*, 639. (m) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1995**, 831. (n) Majewski, M.; Lazny, R. *Synlett* **1996**, 785. (o) Gethin, D. M.; Simpkins, N. S. *Tetrahedron* **1997**, *53*, 14417. (p) Simoni, D.; Roberti, M.; Rondanin, R.; Kozikowski, A. P. *Tetrahedron Lett.* **1999**, *40*, 4425. (q) Majewski, M.; DeCaire, M.; Nowak, P.; Wang, F. *Synlett* **2000**, 1321. (r) Abe, H.; Tsujino, T.: Tsuchida, D.; Kashino, S.; Takeuchi, Y.; Harayama, T. *Heterocycles* **2002**, *56*, 503.

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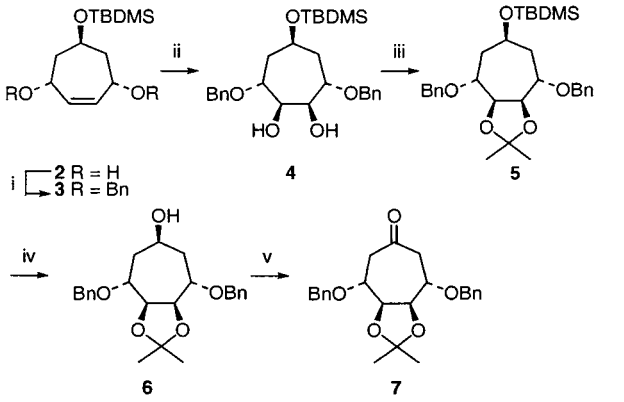
all the carbon units of cycloheptanone should be incorporated into the target compound.

Pseudomonic acids **1a**−**d**, produced by a strain of *Pseudomonas flourescens* as a member of a class of C-glycosides,[4] are known as competitive inhibitors of isoleucyl-tRNA synthetase, and pseudomonic acid A is used clinically for the treatment of bacterial skin infections.[5] Interestingly, these natural products not only possess antibacterial activity against Gram positive bacteria but also display exceptional potency toward multiresistant *Staphylococcus aureus* (MRSA) strains.[5] In view of their attractive biological activities and also the challenging structural features embodying a tetrasubstituted pyran nucleus, a number of chiral syntheses and synthetic approaches to pseudomonic acids have been developed to date,[6] where carbohydrates have mainly been employed as the starting materials, after the first total synthesis of racemic pseudominic acid C by Kozikowski et al.[7] Our own interest in the synthesis of the target compounds grew out of a desire to find a new route for the synthesis of 2,3,4-trisubstituted pyran-5-one, a potential intermediate for the synthesis of pseudominic acid B.

Thus, we applied an enantioselective deprotonation strategy to a *meso*-cycloheptanone derivative having four oxygen functions at the 3,4,5,6-positions that was prepared as depicted in Scheme 1.

Benzylation of diol **2**,[8] readily accessible from tropone, gave dibenzyl ether **3**, which upon dihydroxylation with osmium tetroxide furnished pentaoxygenated compound **4**. After protection of the newly introduced diol system as acetonide **5**, the silyl group was removed by treatment with TBAF to give alcohol **6**. Finally, oxidation of **6** with PCC in the presence of sodium acetate gave the desired *meso*-cycloheptanone **7**.

Scheme 1[a]



[a] Reagents and conditions: (i) BnBr, NaH, TBAI, THF, reflux (94%); (ii) OsO_4, NMO, THF−H_2O, rt (68%); (iii) 2,2-dimethoxypropane, *p*-TsOH, rt (92%); (iv) TBAF, THF, reflux (99%); (v) PCC, NaOAc, 4 Å MS, CH_2Cl_2, rt (94%).

Although various conformations were considered for the cycloheptanone derivative,[9] we used lithium (*S*,*S*′)-α,α′-dimethyldibenzylamide[1d−f] as the chiral base for the enantioselective deprotonation of **7** in order to investigate the mode of enantioselectivity.

Treatment of **7** with lithium (*S*,*S*′)-α,α′-dimethyldibenzylamide in the presence of trimethylsilyl chloride in THF at −78 °C afforded the corresponding silyl enol ether **8**. Since the enantiomeric excess of **8** could not be determined at this stage, **8** was further subjected to oxidative bond cleavage reaction. Ozonolysis of **8**, followed by reductive workup with triphenylphosphine, gave aldehyde **9**, which without purification was further reduced with sodium borohydride to yield alcohol **10** in 92% yield from **7**.

Esterification of acid **10** with iodomethane in DMF in the presence of potassium carbonate furnished ester **11**, whose ee was determined to be 96% by HPLC analysis with the chiral column CHIRALPAK AD.

Although the absolute configuration was still obscure, this result obviously revealed that enantioselective deprotonation is an effective method for introducing a chiral center into even a relatively simple cycloheptanone derivative.

To construct a 2,3,4,5-tetrasubstituted pyran ring system, alcohol **11** was treated with 3 equiv of sodium hexamethyldisilazide at −78 °C in THF, affording two cyclization products **12** and **13** as a mixture of diastereoisomers at the 2-position, where β-elimination of the benzyloxy group, followed by Michael addition of the primary alcohol to the resulting α,β-unsaturated ester, took place simultaneously.[10]

To determine the stereochemistry of the products, including their absolute configurations, deacetalization of **12** and **13** by acid treatment was carried out to afford diol **14** and lactone **15** in 67 and 24% yields, respectively. Thus, the

(3) (a) Honda, T.; Kimura, N. *J. Chem. Soc., Chem. Commun*. **1994**, 77. (b) Honda, T.; Ishikawa, F.; Kanai, K.; Sato, S.; Kato, D.; Tominaga, H. *Heterocycles* **1996**, *42*, 109. (c) Honda, T.; Ono, S.; Mizutani, H.; Hallinan, K. O. *Tetrahedron: Asymmetry* **1997**, *8*, 181. (d) Honda, T.; Endo, K.; Ono, S. *Chem. Pharm. Bull*. **2000**, *48*, 1545. (e) Honda, T.; Endo, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2915 and references therein.

(4) (a) Chain, E. B.; Mellows, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 294. (b) Alexander, R. G.; Clayton, J. P.; Luk, K.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 561. (c) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2827 (d) O'Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2655.

(5) (a) Fuller, A. T.; Mellows, G.; Woolford, M.; Banks, G. T.; Barrow, K. D.; Chain, E. B. *Nature* **1971**, *234*, 416. (b) Basker, M. J.; Comber, K. R.; Clayton, J. P.; Hannan, P. C.; Mizen, L. W.; Rogers, N. H.; Slocombe, B.; Sutherland, R. *Curr. Chemother. Infect. Dis., Proc. Int. Congr. Chemother*. **1979**, *1*, 471. (c) Hughes, J.; Mellows, G. *Biochem. J.* **1978**, *176*, 305. (d) Hughes, J.; Mellows, G.; Southton, S. *FEBS Lett.* **1980**, *122*, 322. (e) Hughes, J.; Mellows, G. *Biochem. J.* **1980**, *191*, 209.

(6) For a review, see: Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843 and references therein. For recent syntheses and synthetic approaches, see: (a) Balog, A.; Yu, M. S.; Curran, D. P. *Synth. Comm*. **1996**, *26*, 935. (b) Khan, N.; Xiao, H.; Zhang, B.; Cheng, X.; Mootoo, D. R. *Tetrahedron* **1999**, *55*, 8303. (c) Markó, I. E.; Plancher, J.-M. *Tetrahedron Lett*. **1999**, *40*, 5259. (d) Mckay, C.; Simpson, T. J.; Willis, C. L.; Forrest, A. K.; O'Hanlon, P. J. *Chem. Commun*. **2000**, 1109. (e) Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4529.

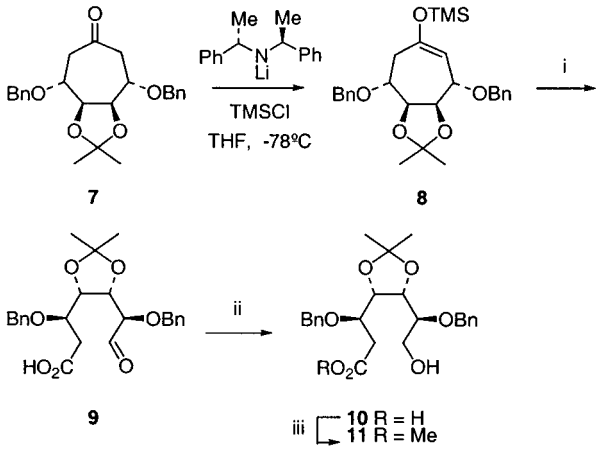
(7) (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc*. **1980**, *102*, 6577. (b) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett*. **1981**, *22*, 2059.

(8) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem*. **1993**, *58*, 7185.

(9) Allinger, N. L.; Chen, K.; Rahman, M.; Pathiaseril, A. *J. Am. Chem. Soc*. **1991**, *113*, 4505 and references therein.

(10) Similar Michael addition was reported in the enantioselective synthesis of pseudomonic acids; see: Schönenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333.

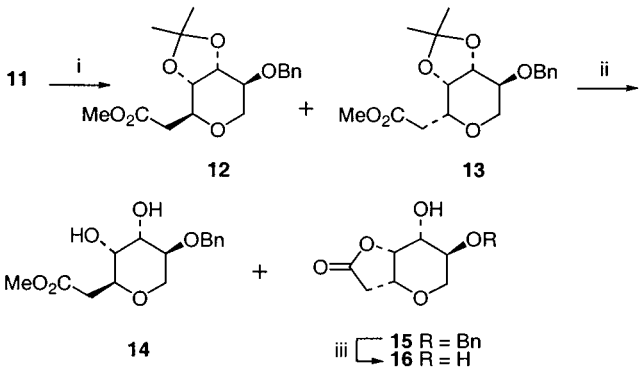
Scheme 2[a]



[a] Reagents and conditions: (i) O_3, MeOH−CH_2Cl_2, −78 °C, then PPh_3, from −78 to 0 °C; (ii) $NaBH_4$, MeOH, rt (92%); (iii) MeI, K_2CO_3, DMF, rt (92%).

major product **14** was confirmed to have the desired stereochemistry. Lactone **15** was further converted into the enantiomer of the known diol **16** by hydrogenolysis over palladium hydroxide. The spectroscopic data of lactone **16** were identical with those reported.[11] Moreover, the sign of optical rotation of our synthetic compound **16** corresponds to those of the antipode,[11] $[\alpha]_D$ +163.6 (*c* 0.1, H_2O) (lit.[11] $[\alpha]_D$ −159.7 (*c* 1.3, H_2O)); therefore, the absolute stereochemistries of both pyrans **12** and **13** are now unambiguously determined as depicted in Scheme 3.

Scheme 3[a]



[a] Reagents and conditions: (i) NaHMDS, THF, −78 °C (73%); (ii) *p*-TsOH, MeOH, rt (67% for **14**, 24% for **15**); (iii) H_2, $Pd(OH)_2$, EtOAc, rt (92%).

Although it was considered, on the basis of examination of molecular models of a substrate having substituents with a cis-relationship at the 4,5-positions of cycloheptanone, that enantioselective deprotonation could proceed through various

(11) Köll, P.; Wernicke, A.; Kovács, J.; Lûtzen, A. *J. Carbohydr. Chem.* **2000**, *19*, 1019.

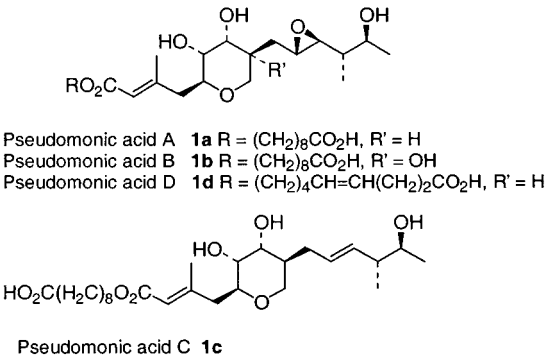


Figure 1.

transition structures,[9] including mainly the conformers TS-1 (twist-chair) and TS-2 (twist-boat), it would be assumed that TS-2 seemed to be favorable relative to TS-1, where unfavorable 1,3-diaxial interactions are observed as depicted in Figure 2.[12] This speculation regarding the conformational

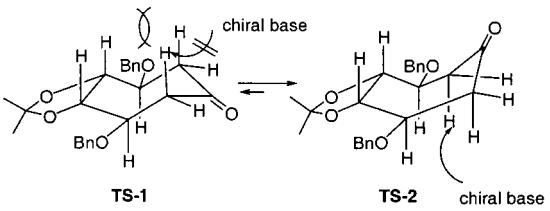


Figure 2.

changes would be consistent with the observed enantioselectivity for prochiral cycloalkanones on the basis of consideration of the previous works.[2,3]

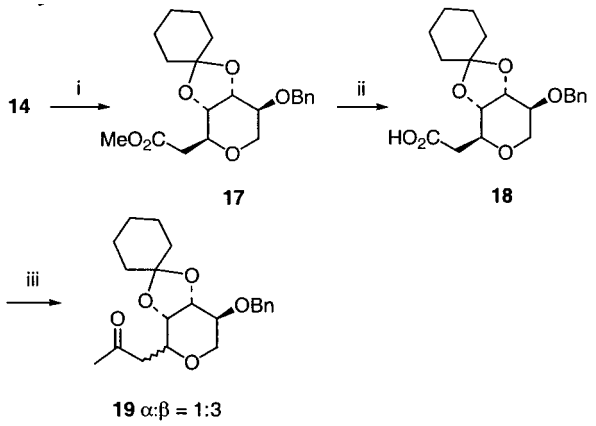
The major compound **14** was further transformed to the known potential intermediate for the synthesis of pseudomonic acid B[13] as shown in Scheme 4.

Treatment of **14** with cyclohexanone and *p*-toluenesulfonic acid gave cyclohexylidene derivative **17**. After hydrolysis of ester **17** in the usual manner, the resulting carboxylic acid **18** was treated with methyllithium at 0 °C to give the desired methyl ketone **19** together with its epimer at the 2-position, probably arising via a retro-Michael reaction, in a ratio of 3:1. Ester **17** was therefore transformed to Weinreb amide **20** prior to introducing a methyl group. Again, treatment of amide **20** with methylmagnesium bromide afforded the

(12) We have examined the conformational stability of compound **7** and its relatives without acetonide or benzyloxy groups by MM2 and MOPAC AM1 methods; however, those calculations revealed that twist-chair conformations are more stable than those of twist-boat forms, as already reported by Allinger.[9] Since those calculations are inconsistent with our experimental results, we are currently investigating the relationships between the conformational stability of cycloheptanone derivatives, including substitution effect and the mode of enantioselectivity.

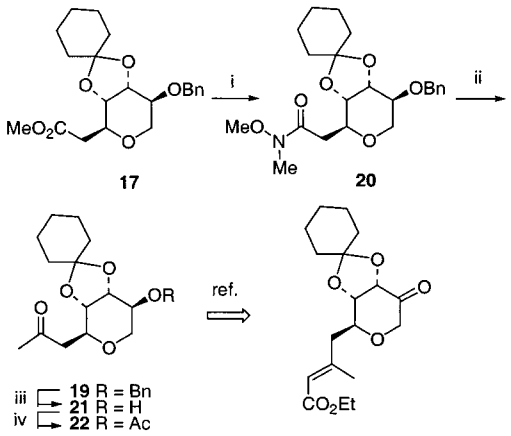
(13) (a) Curran, D. P.; Suh, Y.-G. *Tetrahedron Lett.* **1984**, *25*, 4179. (b) Curran, D. P.; Suh, Y.-G. *Carbohydr. Res.* **1987**, *171*, 161.

Scheme 4[a]



[a] Reagents and conditions: (i) cyclohexanone, $CuSO_4$, *p*-TsOH, benzene, rt (97%); (ii) 2 N KOH, MeOH, rt (93%); (iii) MeLi, Et_2O, 0 °C (42%).

Scheme 5[a]



[a] Reagents and conditions: (i) $Me(OMe)NH_2Cl$, *n*-BuLi, THF, −78 °C (91%); (ii) MeMgBr, THF, 0 °C (92%); (iii) H_2, Pd/C, MeOH, rt (59%); (iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (95%).

desired methyl ketone **19** as the sole product in 92% yield. Finally, debenzylation of **19** under catalytic hydrogenation conditions, followed by acetylation of the resulting alcohol **21** with acetic anhydride, furnished the known acetate **22**, whose spectroscopic data, including the specific optical rotation $[\alpha]_D$ +1.3 (*c* 0.2, $CHCl_3$) (lit.[13b] $[\alpha]_D$ +1.3 (*c* 1.15, $CHCl_3$)), were identical to those reported.[13b] Since this acetate was assumed to be a potential intermediate for pseudomonic acid B,[11] this synthesis provided an alternative approach to this type of biologically important natural product.

In summary, we were able to prove that enantioselective deprotonation was an effective method for introducing chirality into even a relatively simple seven-membered cycloalkanone; we also established a novel synthetic procedure for a potential intermediate in the synthesis of pseudomonic acid B by application of this strategy to a *meso*-cycloheptanone derivative. Further utilization of this procedure in the synthesis of other biologically active compounds, including natural products such as shikimic acid and cyclitols, is in progress in our laboratory.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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