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HIGHLY ENANTIOCONTROLLED TOTAL SYNTHESIS OF (-)-PROTOEMETINOL

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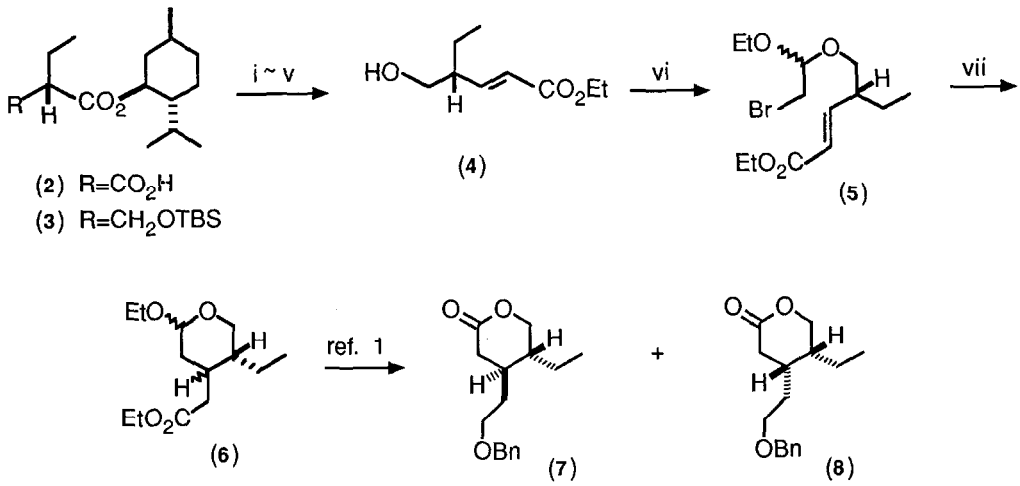
Summary: Enantiomerically pure (-)-protoemetinol (**1**) was selectively synthesized from ethylmalonic acid via radical cyclization of the (Z)-α,β-unsaturated ester (**12**).

Recently a novel synthetic route to the racemate of dihydrocorynantheol was developed via radical cyclization.[1] We further studied on the improvement of the stereoselectivity of the key cyclization and the chiral synthesis of alkaloids by its exploitation. Successful results involving a highly stereocontrolled total synthesis of (-)-protoemetinol (dihydroprotoemetine) (**1**), isolated from Alangium lamarckii,[2] are reported in this communication.

Condensation of ethylmalonic acid with d-menthol accompanied by the crystallization-induced asymmetric transformation of the resulting mono-acid[3] formed a single stereoisomer (**2**), mp 67-70°C, in 74% yield. The acid (**2**) was converted into the silyl ether (**3**) by the modification of the previous procedure.[3] The ester group of **3** was reduced with diisobutylaluminum hydride at -78°C to the corresponding aldehyde, which was reacted with the Wittig reagent to give only the (E)-α,β-unsaturated ester, $[\alpha]_D^{29}$ -4.2° (c=1.57, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ 5.80(1H, dd, J 15.8 and 1.1 Hz, CHCH=CH), 6.79(1H, dd, J 15.8 and 8.6 Hz, CHCH=CH), (73% overall yield) and then desilylated to the primary alcohol (**4**), $[\alpha]_D^{26}$ -8.29° (c=1.01, $CHCl_3$), (98% yield). The optical purity of **4** (> 98% e.e.) was verified by the 500 MHz ^{1}H-NMR spectrum of its (S)-MTPA ester. Treatment of the carbinol (**4**) with ethyl vinyl ether and N-bromosuccinimide[4] followed by radical cyclization of the bromoacetal (**5**), $[\alpha]_D^{24}$ -5.8° (c=0.97, $CHCl_3$), (98% yield), conducting by irradiation (hν ; 2537A) in the presence of $^nBu_3SnH$ at room temperature, gave a mixture of four possible cyclic compounds (**6**) in 96% yield. After transformation of a mixture into the lactones in a similar manner as described previously[1], two lactones (**7** and **8**), obtained in a ratio of about 4:1, were separated by HPLC (Scheme 1). A highly enantioselective synthesis of the desired trans lactone (**7**), $[\alpha]_D^{24}$ +17.46° (c=1.75, $CHCl_3$), was achieved by radical cyclization of the (Z)-

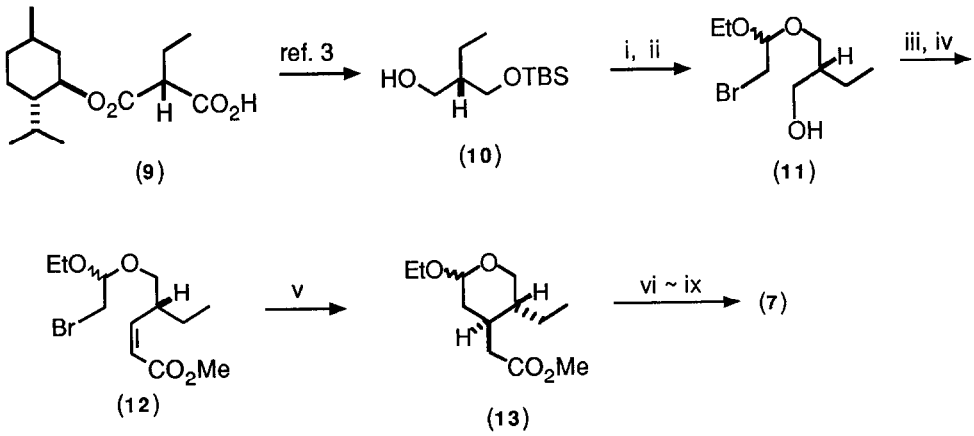
α,β-unsaturated ester (12).



Scheme 1

Reagents: i) $ClCH{=}NMe_2Cl$ then $NaBH_4$. ii) TBSCl, Et_3N, DMAP.
iii) DIBAL-H, -78°C. iv) $Ph_3P{=}CHCO_2Et$. v) $^nBu_4NF$.
vi) NBS, $EtOCH{=}CH_2$. vii) $^nBu_3SnH$, hν.

When the above procedure was applied to the preparation of the (Z)-isomer (12), a lactone formation occurred inevitably during the deprotection of the silyl group. Therefore the unsymmetrical propane-1,3-diol (10), derived from the l-menthyl half ester (9)[3], was firstly reacted with 1,2-dibromoethyl ethyl ether[5] in the presence of N,N-dimethylaniline and then deprotected to afford the alcohol (11) in 88% overall yield. After its conversion into the corresponding aldehyde, the (Z)-α,β-unsaturated ester (12), $[\alpha]_D^{24}$ -30.38° (c=1.17, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ 5.85(1H, d, J 11.9 Hz, CHCH=CH), 6.13(1H, dd, J 11.9 and 9.0 Hz, CHCH=CH), was selectively synthesized in 70% overall yield by the modification of the Still's method.[6] The (E)-isomer formed in less than 10% yield was readily removed by silica gel column chromatography. Radical cyclization of 12 under the same conditions as above produced 88% yield of the ester (13) as a mixture of two anomers, which was converted into the lactone (7) in a good overall yield by the successive treatments; reduction with diisobutylaluminum hydride, benzylation, deblocking and Fetizon's oxidation. No formation of the cis isomer (8) was detected on HPLC and ^{1}H-NMR analyses (Scheme 2). The highly preferential formation of the trans isomers from the (Z)-isomer can be accounted for by the cyclization via the most stable conformation as shown in Figure 1, since other conformations suffer from the heavy allylic strain.



Scheme 2

Reagents: i) $EtOCHBrCH_2Br$, $C_6H_5NMe_2$. ii) $^nBu_4NF$. iii) $(COCl)_2$, DMSO; Et_3N. iv) KH, $(CF_3CH_2O)_2POCH_2CO_2Me$. v) $^nBu_3SnH$, hν. vi) DIBAL-H. vii) NaH, BnBr. viii) AcOH-H_2O (4 : 1 v/v), 60°C. ix) Ag_2CO_3 on Celite.

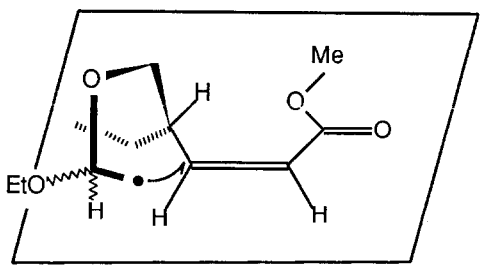
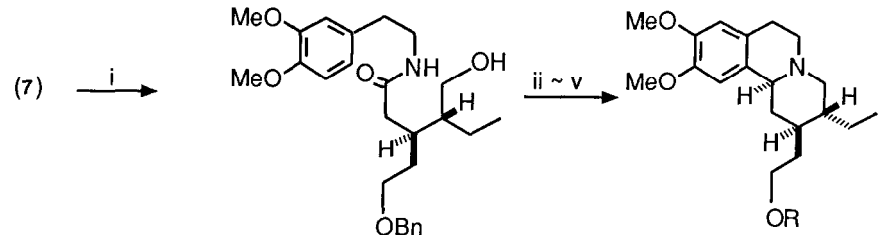


Figure 1.

The specific rotation, $[\alpha]_D^{25}$+16.8° (c=0.5, $CHCl_3$) of (7), prepared from the (Z)-isomer (12), was identical with that of the above specimen within an experimental error; this fact indicated that no racemization took place during the above transformation.

The lactone (7) was further converted into (-)-protoemetinol (1) in a stereoselective manner. Heating (7) with a phenethylamine gave quantitatively the amide (14), $[\alpha]_D^{23}$+6.04° (c=3.82, $CHCl_3$), which was cyclized[7] to the iminium salt and then reduced by catalytic hydrogenation using Adams catalyst.[8,9] Deprotection of the trans quinolizidine (15), selectively obtained in 51% overall yield, furnished protoemetinol (1), which was converted into the perchlorate, mp 202-204°C (lit.,[8] mp 199-200°C), $[\alpha]_D^{24}$-15.27° (c=0.26, MeOH). The NMR spectrum of the free base (1) was identical with that of the authentic racemate.[10]



(14)

(15) R=CH_2Ph

(1) R=H

Scheme 3

Reagents: i) 2-(3,4-dimethoxyphenyl)ethylamine, 135°C. ii) $POCl_3$. iii) $LiClO_4$. iv) H_2, PtO_2. v) H_2, $PdCl_2$, $CHCl_3$-EtOH (1 : 25 v/v).

Thus a highly enantioselective total synthesis of (-)-protoemetinol was accomplished. It should be noticed that the above lactone (**7**) is a potential key intermediate for the synthesis of a number of ipecacuanha alkaloids and indole alkaloids. Furthermore this work demonstrated a usefulness of our asymmetric synthesis of propane-1,3-diol derivatives from malonic acid.[3]

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