AN ASYMMETRIC SYNTHESIS OF A QUATERNARY CHIRAL BUILDING BLOCK FROM ETHYLMALONIC ACID: A PREPARATION OF KEY SYNTHETIC INTERMEDIATES OF HUNTERIA- AND ASPIDOSPERMA-TYPE INDOLE ALKALOIDS

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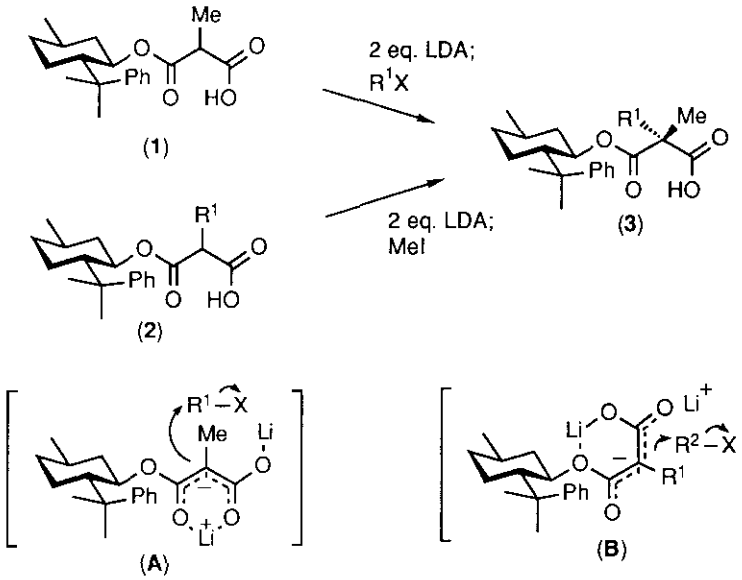
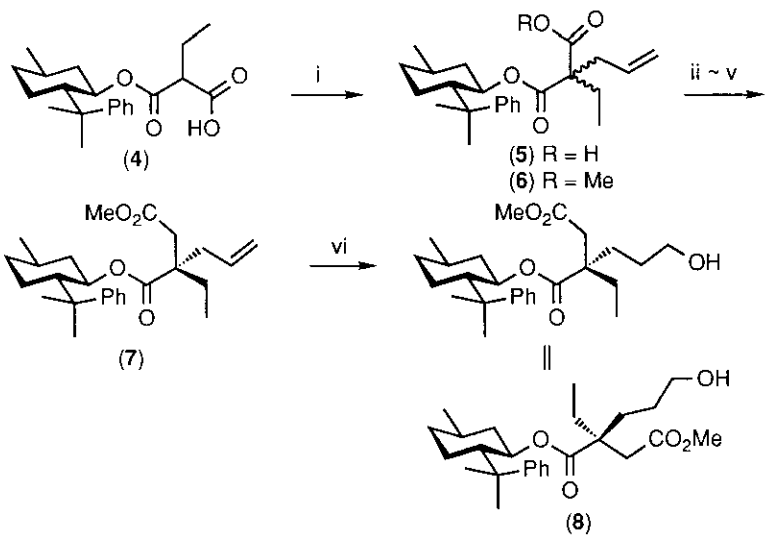
Abstract -- The major product, obtained by allylation of the (-)-phenylmenthyl half ester (**4**) of ethylmalonic acid, was converted into two lactones (**11**) and (**16**), the key intermediates for indole alkaloids of *Hunteria*- and *Aspidosperma*-type.

A new method for a construction of a quaternary asymmetric carbon center by reaction of dianions, derived from chiral half esters of monosubstituted malonic acids, with alkyl halides was disclosed in our recent communication.[1] Thus alkylation of the(-)-phenylmenthyl half ester (**1**) of methylmalonic acid produced mainly the (R)-isomer (**3**), which would be formed via the transition state (**A**). It was further noteworthy that the same diastereoisomers (**3**) were major products on methylation of the half esters (**2**). It was supposed that the geometry (**A**) became disfavoured at the early or



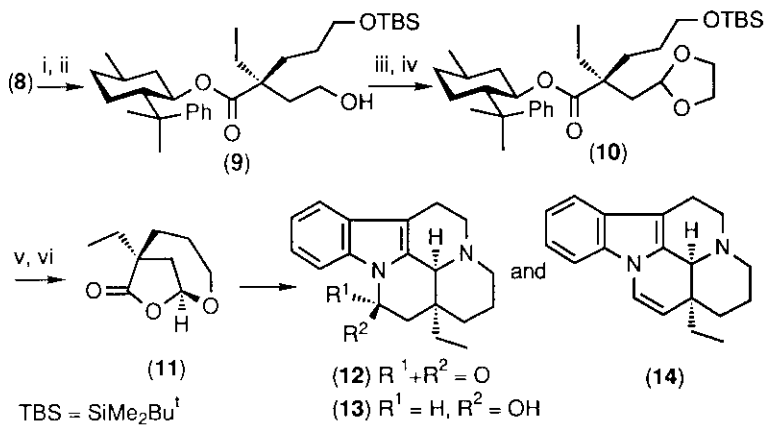
late transition state,[2] and the other one (**B**) would be more important for alkylation of half esters except the methylmalonate (**1**).[3] Allylation of the half ester (**4**) of ethylmalonic acid was then carried out from the mechanistic as well as synthetic interest and we wish to report a support for the geometry (**B**) and an asymmetric synthesis of key intermediates (**11**)[4,5] and (**16**)[5] for indole alkaloids.

In expectation of preferred formation of the (S)-isomer from the consideration of the above result in methylation of (**2**), the (-)-phenylmenthyl half ester (**4**)[1] of ethylmalonic acid was converted, with excess lithium diisopropylamide (LDA), into the dianion, which was reacted for 3 h with allyl iodide at -78 ~ -50 °C in tetrahydrofuran. The ratio of two diastereoisomers of the alkylated products (**5**), obtained quantitatively, was determined as 2.6:1 by 500 MHz ^{1}H nmr spectroscopy after conversion using diazomethane into the methyl ester (**6**). The epimeric mixture (**5**) was reacted with oxalyl chloride in the presence of pyridine to give the acid chloride, which was treated with diazomethane. The formed diazoketone was irradiated in methanol through Pyrex filter with 400W high-pressure mercury lamp to afford, in 76% overall yield for three steps, the methyl ester, whose major isomer, (**7**), $[\alpha]_D^{23}$ -4.85° (c 1.03 in $CHCl_3$) was isolated by hplc technique. Hydroboration of (**7**) using dicyclohexylborane, followed by oxidation, provided the primary carbinol (**8**), $[\alpha]_D^{26}$ -13.18° (c 1.55 in $CHCl_3$), in 92% yield.



Reagents and conditions: i, > 2 eq. LDA then CH_2=$CHCH_2I$, -78~-50 °C; ii, $(COCl)_2$, pyridine; iii, CH_2N_2; iv, hv, MeOH; v, HPLC; vi, dicyclohexylborane then H_2O_2, NaOH.

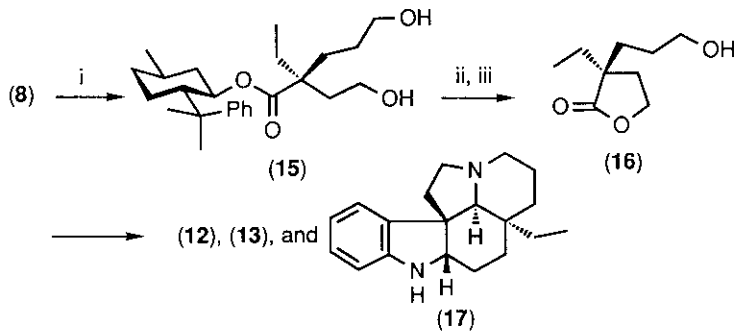
The methyl ester (**8**) was first transformed into the bicyclic lactone (**11**)[4,5] as follows. Protection of the hydroxyl group of (**8**) with dimethyl-t-butylsilyl group (93% yield), followed by reduction of the resulting compound with diisobutylaluminium hydride (DIBAL), gave the hydroxyl ester (**9**), $[\alpha]_D^{22}$ -8.40° (c 3.44 in $CHCl_3$), in 76% yield. After Swern oxidation of (**9**), the aldehyde was converted into the acetal (**10**), $[\alpha]_D^{23}$ -12.67° (c 0.43 in $CHCl_3$), in 79% overall yield for two steps. The phenylmenthyl group of (**10**) was deblocked with potassium superoxide in the presence of 18-Crown-6[6] in refluxing benzene and the formed acid was treated with perchloric acid in hot tetrahydrofuran to give the bicyclic lactone (**11**), mp 79 - 82 °C, $[\alpha]_D^{24}$ +8.16° (c 0.49 in CH_2Cl_2), [lit.[4] mp 82 - 85 °C, $[\alpha]_D$ +6.7° (c 0.42 in CH_2Cl_2); lit.[5] mp 89 - 90 °C, $[\alpha]_D^{22}$ +5.4°(c 1.47 in CH_2Cl_2)], in 58% overall yield. Thus the absolute configuration of the major product on allylation was determined and the fact supported the geometry (**B**) of the transition state. The bicyclic lactone (**11**), whose spectral data were identical with those of the authentic sample,[4] had been correlated with (-)-eburnamonine (**12**), (+)-eburnamine (**13**), and (-)-eburnamenine (**14**).[4]



Reagents and conditions: i, TBSCl, Et_3N, DMAP; ii, DIBAL; iii, DMSO, $(COCl)_2$ then Et_3N; iv, $HOCH_2CH_2OH$, CSA, heat; v, KO_2, 18-Crown-6, heat; vi, $HClO_4$, heat.

Next, the above methyl ester (**8**) was converted into the lactone (**16**) by the following straightforward sequence. Reduction of (**8**) with DIBAL gave, in 72% yield, the diol (**15**), $[\alpha]_D^{24}$ -13.59° (c 2.67 in $CHCl_3$), whose phenylmenthyl group was removed by potassium superoxide in the presence of 18-Crown-6 at room temperature. The lactone (**16**), $[\alpha]_D^{22}$ +1.85° (c 1.10 in $CHCl_3$), was obtained in 87% overall yield for two steps after treatment of the crude acid with refluxing 9% hydrochloric acid. The lactone (**16**), whose spectral data were superimposable on those of the authentic

compound (**16**),[5] had been transformed into (-)-eburnamonine (**12**), (+)-eburnamine (**13**), and (-)-aspidospermidine (**17**).[5]



Reagents and conditions; i, DIBAL; ii, KO_2, 18-Crown-6, room temp.; iii, dil. HCl, heat.

Thus two intermediates (**11**) and (**16**) for the synthesis of *Hunteria*- and *Aspidosperma*-type indole alkaloids were prepared from ethylmalonic acid via the allylation of the chiral half ester.

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REFERENCES AND NOTE

1. M. Ihara, M. Takahashi, H. Niitsuma, N. Taniguchi, K. Yasui, and K. Fukumoto, *J. Org. Chem.*, 1989, **54**, 5413.

2. C. M. Lentz and G. H. Posner, *Tetrahedron Lett.*, 1978, 3769; T. Takahashi, M. Nisar, K. Shimizu, and J. Tsuji, *Tetrahedron Lett.*, 1986, **27**, 5103; K. Tomioka, H. Kawasaki, K. Yasuda, and K. Koga, *J. Am. Chem. Soc.*, 1988, **110**, 3597.

3. A similar geometry was recently proposed for Michael addition of the α-formyl ester derived from 2-(1-naphthyl)-3-borneol. D. F. Taber, J. F. Mack, A. L. Rheingold, and S. J. Geib, *J. Org. Chem.*, 1989, **54**, 3831.

4. S. Takano, M. Yonaga, M. Morimoto, and K. Ogasawara, *J. Chem. Soc., Perkin Trans. 1*, 1985, 305.

5. M. Node, H. Nagasawa, and K. Fuji, *J. Am. Chem. Soc.*, 1987, **109**, 7901.

6. J. San Filippo, Jr., L. J. Romano, C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, 1976, **41**, 586.

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