Asymmetric Induction Studies in the Synthesis of Bicyclic Sesquiterpenes: Attempted Synthesis of (−)-Drimenol

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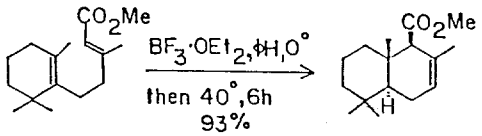
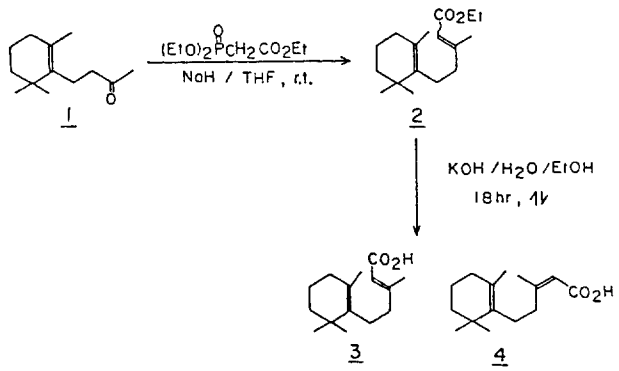
Chiral auxiliaries were used in many different types of reactions[1] for asymmetric synthesis of natural products. We became interested in the use of optically active 1,1'-bi-2-naphthol as a chiral auxiliary in the acid catalyzed polyene cyclization reactions typified by the efficient conversion of methyl monocyclofarnesate to methyl bicyclofarnesate of drimane skeleton.[2] (Scheme 1)



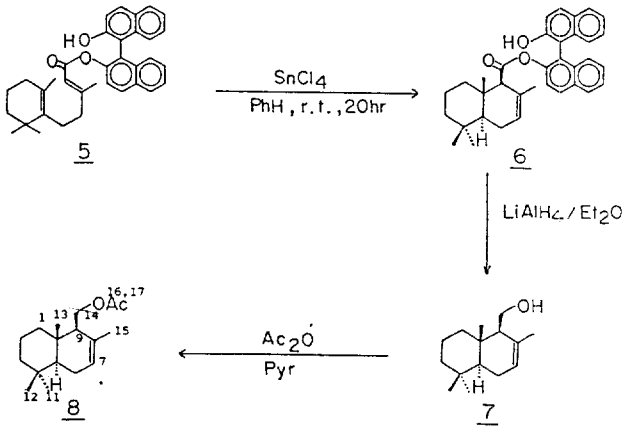
Scheme 1

Dihydro-β-ionone(**1**) was prepared from β-cyclocitral in conventional ways: reduction to the alcohol by sodium borohydride, conversion to the allylic bromide by reaction with phosphorus tribromide and calcium hydride,[3] substitution by ethyl sodioacetoacetate, and decarboxylation in wet dimethyl sulfoxide containing sodium chloride.[4] Reaction of **1** with triethyl phosphonoacetate gave a mixture of (*E*)- and (*Z*)-isomers of ethyl monocyclofarnesate(**2**).[2] (*E*:*Z* = ≈4:1) The mixture was directly hydrolyzed to give predominantly (*E*)-monocyclofarnesic acid(**3**). (*E*:*Z* = ≈8:1) In the nmr spectra, the signal for the methyl group attached to the β carbon of the (*E*)-acid(**3**) appeared at δ 2.18 while that of the (*Z*)-acid(**4**) was found at δ1.97. (Scheme 2)



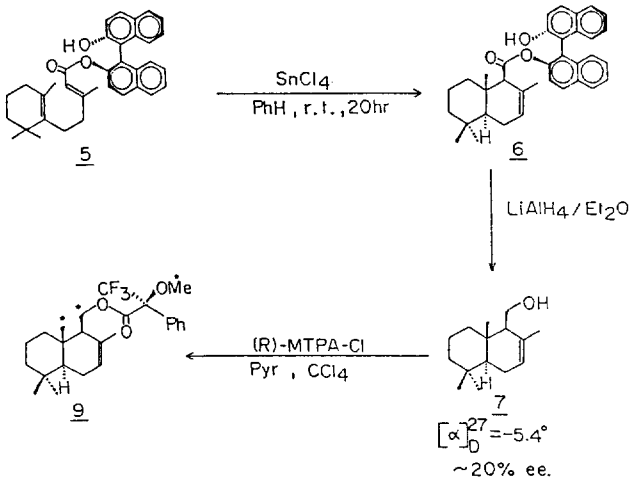
Scheme 2

Esterification of (*E*)-monocyclofarnesic acid(**3**) with racemic 1,1'-bi-2-naphthol was readily accomplished by conversion to the acid chloride and treatment of the acid chloride with (±)-1,1'-bi-2-naphthol in dichloromethane and pyridine. The nmr spectrum of racemic (*E*)-binaphthyl ester **5**[5] showed that non-aromatic proton signals in **5** shifted upfield by 0.15-0.17 ppm compared to those of the ethyl ester **2** suggesting noticeable anisotropic influence of the naphthalene moiety on the non-aromatic part of the molecule.



Scheme 3

Treatment of the racemic ester **5** in benzene with boron trifluoride etherate resulted mainly in the hydrolysis and the cyclized product was obtained in a poor (≈10%) yield. However, when **5** was reacted with **2** equivalents of stannic chloride in benzene for 20 hours at room temeprature, the desired bicyclic product **6** was obtained in 40% yield after silica gel column chromatography. (Scheme 3) Subsequent reaction with lithium aluminum hydride resulted in the formation of drimenol(**7**) as a single product accompanied by recovered 1,1'-bi-2-naphthol. The structure of **7** was confirned by extensive spectroscopic data on the corresponding acetate **8**.[6] In particular, ^{13}C chemical shift value of the carbon-13 of **8** (δ 14.4) was diagnostic; known values for the corresponding carbons of drimenol and 9-epidrimenol are δ 14.8 and δ 23.1, respectively.[7] The origin of the high stereoselectivity observed in this type of cyclization reactions was already discussed in the literature.[8]



Scheme 4

For the chiral induction experiment, (*R*)-(+)-1,1′-bi-2-naphthol was used to prepare the optically active monofarnesate ester (*R*)-**5**. Cyclization of (*R*)-**5** and the reduction of the resultant (*R*)-**6** with lithium aluminum hydride yielded optically active drimenol (−)-**7**. ($[\alpha]_D^{27} = -5.4°$, $c = 0.41$, benzene; literature value,[9] $[\alpha]_D^{17} = -19.1°$, $c = 0.76$, benzene) Analysis of the high resolution nmr spectrum[10] of the ester **9** prepared from (−)-**7** and (*R*)-MTPA chloride led to a more dependable optical purity value (20% *e.e.*) of the product. (Scheme 4)

In conclusion, use of optically active 1,1′-bi-2-naphthol as a chiral auxiliary in the acid catalyzed cyclization of monocyclofarnesate resulted in a moderately low chiral induction. Employment of other chiral agents for more efficient asymmetric synthesis of this important class of compounds will be the subject of future studies.

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References

1. For general reviews, see: "Asymmetric Synthesis", Vol. 2 & Vol. 3, J. D., Morrison, Ed.; Academic Press: New York, 1983 & 1984.
2. C. Schmidt, N. H. Chishti, T. Breining, Synthesis, 391 (1982). Note the error the above authors made concerning the configuration at C-9 of methyl bicyclofarnesate.
3. B. M. Trost, M. J. Bogdanowicz, W. J. Frazee, T. N. Salzmann, *J. Am. Chem. Soc.* **100,** 5512 (1978).
4. A. P. Krapcho, Synthesis, 893 (1982).
5. A small amount of (*Z*)-binaphthyl ester was also formed in the esterification step, which was removed via silica gel column chromatography.
6. The structure of the acetate **8** was confirmed by extensive spectroscopic analysis including attached proton test and ^{13}C-^{1}H chemical shift correlation spectrum: ^{1}H nmr ($CDCl_3$, 360 MHz) δ 0.81(s, 3H), 0.86(s, 3H), 0.88(s, 3H), 1.05-1.25(m, 5H), 1.45(m, 2H), 1.66(s, 3H), 1.90-2.05(m, 3H), 2.03(s, 3H), 4.07(dd, J = 12 and 6 Hz, 1H), 4.24(dd, J = 12 and 3 Hz, 1H), 5.49(m, 1H); ^{13}C nmr ($CDCl_3$, 360 MHz) δ 14.43(C-13), 18.69(C-2), 21.20 (C-17), 21.66(C-15), 21.89(C-12), 23.57(C-6), 32.92(C-4), 33.26(C-11), 35.92(C-10), 39.52(C-1), 42.06(C-3), 49.83 (C-5), 53.35(C-9), 63.15(C-14), 123.63(C-7), 132.44(C-8), 171.08(C-16). See also: "Interpretation of Carbon-13 NMR Spectra", F. W. Wehrli; T. Wirthlin,; Heyden: London, p. 44 (1978)
7. M. Nishizawa, H. Takenaka, Y. Hayashi, *Tetrahedron Lett.* **25,** 437 (1984).
8. K. E. Harding, *Bioorganic Chem.* **2,** 248 (1973).
9. "Dictionary of Organic Compounds", 5th Ed., Vol. 3, Chapman and Hall: New York, p. 2406, (1982)
10. In the ^{1}H nmr spectrum ($CDCl_3$, 360 MHz) of the MTPA ester **9**, protons on C-13 and C-14 exhibited split signals in addition to the split signals for the methoxy protons of the MTPA moiety. These were used in the determination of optical purity of the sample. Note that (*S*)-(−)-MTPA acid is converted to (*R*)-MTPA chloride, which is used for the synthesis of (*S*)-MTPA esters.

Unusual "Lewis Acid" Effect on the Photodimerization of 4,5′,8-Trimethylpsoralen(TMP)

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Many reactions of α,β-unsaturated carbonyl and nitrile compounds are catalysed by Lewis acids. These include, for example, catalyzed Diels-Alder reactions, alternating copolymerizations, [2+2] cycloadditions, aldol condensations, and several photoreactions. Especially in Diels-Alder and ene reactions, the enhanced reactivity and stereoselectivity have been attributed to changes in frontier orbital energies and C=C double bond polarity upon complexation of the carbonyl oxygen.[1] Lewis *et al.* have reported that Lewis acid complexation of α,β-unsaturated esters results in marked changes in their spectroscopic properties and unimolecular photochemistry.[2] The possibility that Lewis acids might also serve as catalysts for bimolecular photochemical reactions is suggested by reports concerning the photodimerization of dibenzylideneacetone in the presence of $SnCl_4$[3], by preliminary reports concerning the effect of Lewis acids on the photodimerization of coumarin[4(a)] and cinnamic esters,[4(b)] and by a recent report of selective head-to-head dimerization of cyclopentenone in the presence of $SnCl_4$[5].

We have initiated a study on the photodimerization of a biologically important furocoumarins in the presence of Lewis acids. Because of the importance of psoralens(furocoumarins) in the treatment of psoriasis and vitiligo, the photophysical properties of the lowest excited states(singlet and triplet) of furocoumarins and coumarins have been extensively investigated in recent years.[6] The excited states of 4,5′,8-trimethylpsoralen(TMP) have been investigated in rigid matrices at 12 and 77K by means of luminescence and