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THE ASYMMETRIC DIELS-ALDER REACTIONS OF α,β-UNSATURATED CARBOXYLIC AMIDES DERIVED FROM (-)-PHENYLGLYCINOL AND THE ASYMMETRIC TOTAL SYNTHESIS OF (+)-FARNESIFEROL C

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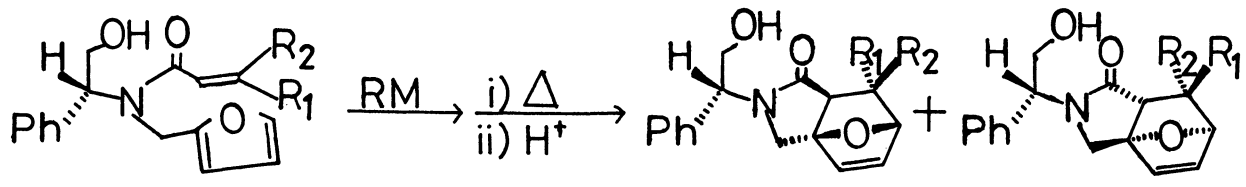
The asymmetric intramolecular Diels-Alder reactions of α,β-unsaturated carboxylic amides derived from (-)-phenylglycinol were studied and successfully applied to the asymmetric total synthesis of (+)-farnesiferol C.

We recently reported an efficient method for the acceleration of the intramolecular Diels-Alder reactions utilizing the internal coordination of the magnesium salts.[1] In the present communication, we wish to report the asymmetric intramolecular Diels-Alder reactions and their application to the asymmetric total synthesis of (+)-farnesiferol C, an antipode of natural one.

The asymmetric Diels-Alder reactions using chiral dienes or dienophiles, or the employment of chiral Lewis acids as promotors have been extensively studied during these years.[2] However, the intramolecular Diels-Alder reactions with chiral sources in the molecules have not been sufficiently investigated so far.[3]

It was expected that the internal chelate formation in amide 1 would fix the molecule and lead both to the effective transfer of chirality and to the acceleration of the reaction. When a toluene solution of optically active (-)-phenylglycinol derivative 1a was refluxed for 50 hours, equal amounts of two diastereomeric cycloadducts 2a[9] and 3a[9] were obtained in 48% yield. On the other hand, when the toluene solution of the magnesium salt of 1a was refluxed for 7 hours, 2a and 3a were obtained in 77% yield and the diastereomeric ratio of the products became 88% and 12%, respectively. These two diastereomers could be easily separated by silica gel column chromatography. Similar results were also obtained when crotonamide derivatives were employed as dienophiles. [See Table]



1a,b 2a,b 3a,b

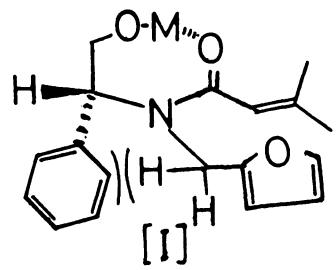
a: $R_1 = R_2 = Me$
b: $R_1 = Me$, $R_2 = H$

Table The Diels-Alder reactions of 1a and 1b[a]

compound	salt	reaction time	yield	diastereomeric ratio 2:3
1a	-OH	50	48	50:50
1a	-OMgCl	7	86	86:14
1a	-OMgBr	7	77	88:12
1a	-OMgI	7	72	81:19
1b	-OH	3.25	57	57:43
1b	-OMgCl	3.25	82	83:17

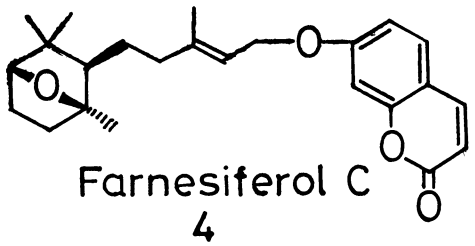
a) Refluxed in toluene.

The selectivity could be explained by considering the steric repulsion between benzene ring and methylene group next to the furan in the chelate complex [I]. To minimize the steric interaction, the approach of the furan nucleus to the dienophiles takes place preferentially from the opposite side of the benzene ring.



[I]

Farnesiferol C is a sesquiterpene isolated from Asa foetida, and its absolute configuration was deduced as depicted in 4.[4]



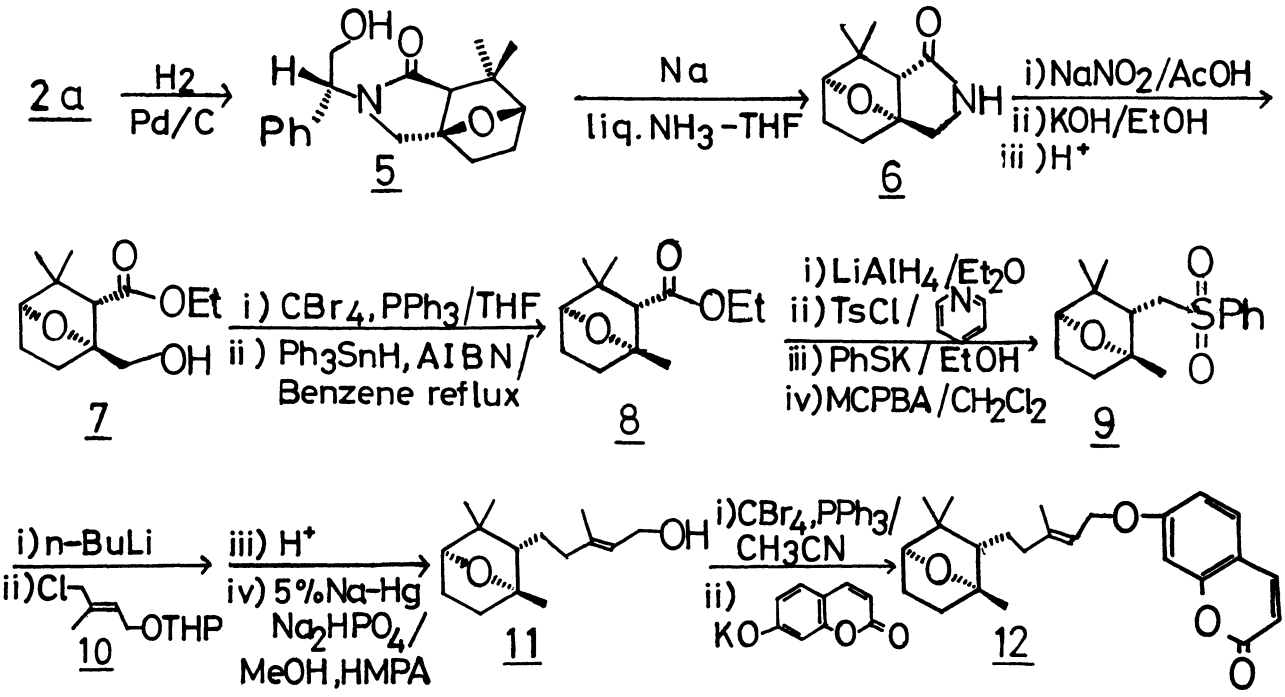
Farnesiferol C
4

In order to transform the above cycloadduct 2a into farnesiferol C, it is necessary to remove the phenylglycinol part which is introduced to bring forth asymmetry. Noting that benzylic amines are susceptible to hydrogenolysis, we tried to cleave this group under various conditions, but only hydrogenated product 5[9] was obtained or in some cases aromatic nucleus was reduced. Finally, it was found that the reduction is successfully achieved by treating the hydrogenated compound 5 with Na in liquid ammonia and THF at -78°C. Thus γ-lactam 6[9] was obtained in 78% yield after purification by silica gel column chromatography.

γ-Lactam 6 was nitrosated with sodium nitrite in acetic acid and acetic anhydride and then converted to the hydroxyester 7[5),6),9)] in 81% yield from 6. This hydroxyl group was removed by bromination (CBr_4-PPh_3 in THF at 0°C) and tin hydride reduction (Ph_3SnH, benzene reflux, AIBN) to give ester 8[9] in 78% yield.

In order to introduce the olefinic side chain, the ester 8 was converted to the sulfone 9[9] by the following treatments; (I) reduction with $LiAlH_4$ in ether at 0°C, (II) tosylation of the hydroxyl group with TsCl in pyridine at 0°C, (III) thiophenylation of the tosylate with PhSK in EtOH at room temperature, (IV) oxidation of the sulfide with MCPBA at room temperature. The overall yield of these four steps was 92%. The sulfone 9 was lithiated with n-BuLi at -78°C in the presence of HMPA and then THP-protected allyl chloride 10 was added. The reaction mixture was slowly warmed to room temperature and stirred overnight.

Without purification of the product, the tetrahydropyranyl group was removed with dilute hydrochloric acid in MeOH and then sulfonyl group was also cleaved using 5% Na-Hg in HMPA and MeOH at 0°C in the presence of Na_2HPO_4.[7] Thus allyl alcohol 11[9] was obtained in 50% yield from 9. At the end of this synthesis, the allyl alcohol 11 was brominated with CBr_4-PPh_3 in acetonitrile at 0°C for one hour and then potassium salt of umbelliferone was added to this reaction mixture and further stirred at 0°C overnight. After purification by thin layer chromatography, farnesiferol C 12[9] (the antipode of natural product as shown by the specific rotation $[\alpha]_D^{24}$+31.7°) was obtained in 76% yield. The result indicates that natural farnesiferol C is available by the present scheme by using L-(+)-phenylglycine[8].



Acknowledgment

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References and Notes

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2) S. Hashimoto, N. Komeshima, and K. Koga, J. Chem. Soc., Chem. Comm., 1979, 437; and references cited therein.

3) S. G. Pyne, M. J. Hensel, S. R. Byrn, A. T. McKenzie, and P. L. Fuchs, J. Am. Chem. Soc., 102, 5960 (1980).

4) L. Caglioti, H. Naef, D. Arigoni, and O. Jeger, Helv. Chim. Acta, 41, 2278 (1958); ibid., 42, 2257 (1959); E. E. van Tamelen and R. M. Coates. Chem. Comm., 13, 413 (1966).

5) T. Mukaiyama, N. Iwasawa, T. Tsuji, and K. Narasaka, Chem. Lett., 1979, 1175.

6) To avoid lactonization, it is necessary to keep the reaction medium about pH 7 during the decomposition of diazocarboxylic acid with 2N hydrochloric acid.

7) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, Tetrahedron Lett., 1976, 3477.

8) C. S. Marvel and W. A. Noyes, J. Am. Chem. Soc., 42, 2259 (1920).

9) Analytical data of these compounds are as follows;
cycloadduct 2a: mp 155.5-156.5°C(ethyl acetate); IR(KBr) ν=3490, 1675 cm^{-1}; NMR($CDCl_3$) δ=1.02(3H,s), 1.38(3H,s), 2.10(1H,s), 3.20(1H,br), 3.40(1H,d,J=12Hz), 3.85(1H,d,J=12Hz), 3.90-4.13(2H,m), 4.30(1H,s), 5.17(1H,dd,J=8Hz, 6Hz), 6.30(2H,s), 7.13(5H,s); $[\alpha]_D^{25}$-85.1°(c 6.61, methanol).
cycloadduct 3a: mp 164.5-165.0°C(ethyl acetate); IR(KBr) ν=3440, 1655 cm^{-1}; NMR($CDCl_3$) δ=1.00(3H,s), 1.40(3H,s), 2.03(1H,s), 3.13(1H,t,J=6Hz), 3.45(2H,s), 3.85-4.13(2H,m), 4.30(1H,s), 5.00(1H,t,J=7Hz), 6.23(2H,s), 7.13(5H,s); $[\alpha]_D^{23}$-130.2° (c 6.65, methanol).
hydrogenated compound 5: mp 117.0-118.0°C(cyclohexane); IR(KBr) ν=3490, 1680 cm^{-1}; NMR($CDCl_3$) δ=1.18(3H,s), 1.23(3H,s), 1.63-2.00(4H,m), 2.20(1H,s), 3.37(1H,br), 3.37(1H,d,J=11Hz), 3.57(1H,d,J=11Hz), 3.83-4.17(3H,m), 5.10(1H, dd, J=8Hz, 5Hz), 7.13(5H,s); $[\alpha]_D^{24}$-53.1°(c 3.39, methanol).
γ-lactam 6: mp 153.0-153.5°C(benzene and cyclohexane); IR(KBr) ν=3380, 1695, 1655 cm^{-1}; NMR($CDCl_3$) δ=1.17(3H,s), 1.23(3H,s), 1.67-1.83(4H,m), 2.00(1H,s), 3.46(2H,s), 3.86(1H,d,J=3Hz), 5.13(1H,br); $[\alpha]_D^{28}$+88.3°(c 3.94, ethanol).
hydroxyester 7: IR(neat) ν=3450, 1735 cm^{-1}, NMR($CDCl_3$) δ=1.02(3H,s), 1.18(3H,s), 1.23(3H,t,J=7Hz), 1.60-1.90(4H,m), 2.34(1H,s), 2.93(1H,br), 3.83-4.20(5H,m); $[\alpha]_D^{26}$+35.2°(c 3.55, benzene).
ester 8: IR(neat) ν=1740 cm^{-1}; NMR($CDCl_3$) δ=1.03(3H,s), 1.17(3H,s), 1.23(3H, t,J=7Hz), 1.52(3H,s), 1.55-2.00(4H,m), 2.27(1H,s), 3.80(1H,d,J=4Hz), 4.05(2H, q,J=7Hz); $[\alpha]_D^{23}$+8.1°(c 3.22, benzene).
sulfone 9: mp 72.0-73.0°C(benzene and cyclohexane); ν=1305, 1145 cm^{-1}; NMR($CDCl_3$) δ=1.05(3H,s), 1.07(3H,s), 1.30(3H,s), 1.50-2.00(5H,m), 3.10(2H,d,J=6Hz), 3.70 (1H,d,J=4Hz), 7.50-7.93(5H,m); $[\alpha]_D^{23}$+31.2°(c 1.73, ethanol).
allyl alcohol 11: IR(neat) ν=3400, 1660 cm^{-1}; NMR($CDCl_3$) δ=0.98(3H,s), 1.03(3H, s), 1.30(3H,s), 1.63(3H,s), 1.17-2.10(10H,m), 3.62(1H,d,J=4Hz), 4.03(2H,d,J=7Hz), 5.27(1H,t,J=6Hz); $[\alpha]_D^{23}$+38.1°(c 4.04, benzene).
Farnesiferol C 12: mp 84.0-84.5°C(ether and hexane), IR(KBr) ν=1700, 1610 cm^{-1}; NMR($CDCl_3$) δ=1.03(3H,s), 1.05(3H,s), 1.33(3H,s), 1.77(3H,s), 1.17-2.17(9H,m), 3.70(1H,d,J=4Hz), 4.58(2H,d,J=6Hz), 5.45(1H,t,J=6Hz), 6.15-7.67(5H,m); $[\alpha]_D^{24}$+ 31.7°(c 0.78, chloroform).

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