A NEW ROUTE TO QUASSIN BASIC SKELETON VIA ALLENECARBOXYLATE INTRAMOLECULAR CYCLOADDITION

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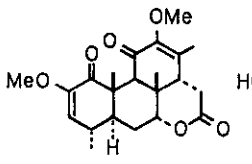
Abstract - The new route to quassin basic skeleton, tetracyclic lactones has been realized via the intramolecular Diels-Alder reaction of allene-1,3-dicarboxylates.



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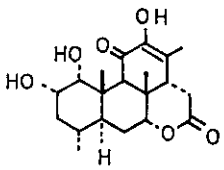

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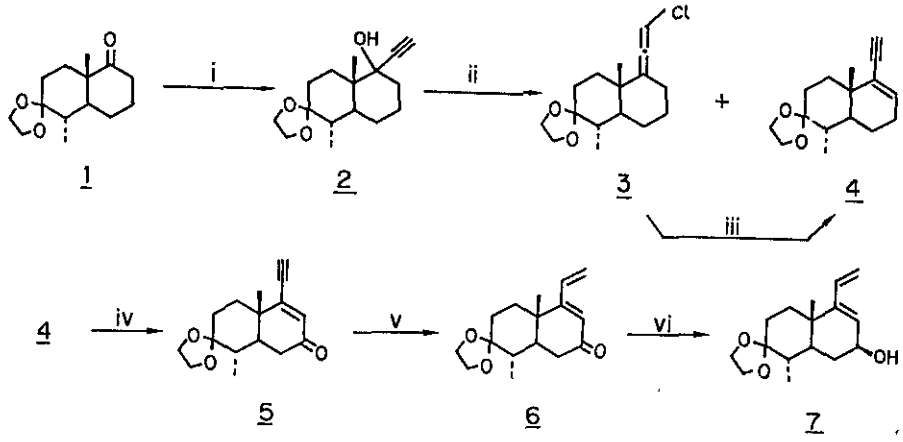
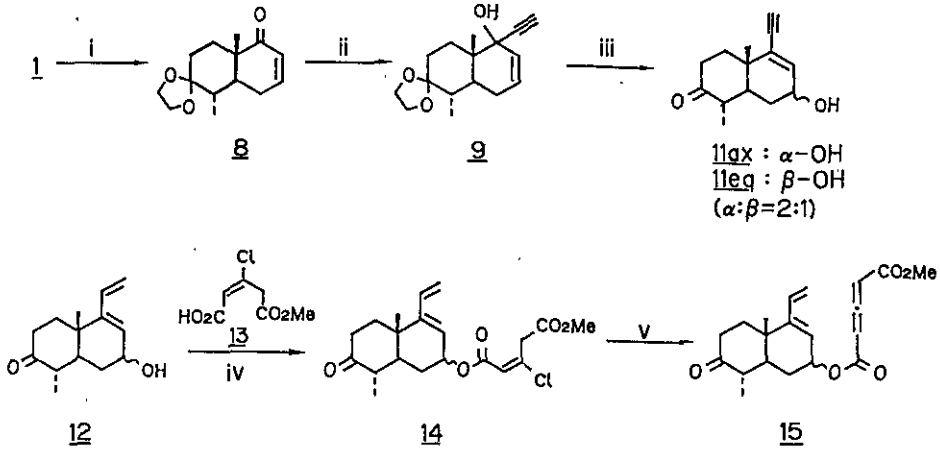
The quassinoids, a group of related triterpenoids found in plants of the family Simaroubaceae, possess a wide spectrum of biological activity.[1] Quassin (A) and castelanolide (B) were elegantly synthesized via intermolecular Diels-Alder reaction by Grieco's group.[2] However, despite the efforts of numerous synthetic groups, the total synthesis of bruceantin or quassimarin has yet to be synthesized.[3] Previously, we reported the periselective intramolecular cycloaddition reaction of allenecarboxylates, in which we demonstrated the synthesis of tricyclic six-membered lactones.[4] We now wish to report a new synthesis of quassin basic skeleton via intramolecular Diels-Alder reaction of allene-1,3-dicarboxylates.

The allene-1,3-dicarboxylates were prepared as follow. Reaction of the known ketone (1) derived from Wieland-Miescher diketone with a large excess of the ethylenediamine complex of lithium acetylide at -78°C for 3 days gave acetylenic alcohol (2) in 66% yield. Dehydration of the alcohol (2) afforded a 2:3 mixture of compounds (3) and (4) in 54% yield. The chloroallene (3) was converted to the desired compound (4) by thermal treatment with DBU in 73% yield. Allylic oxidation of 4 was carried out with a 3,5-dimethylpyrazole complex of chromium trioxide, generated in situ, to give enone (5) in 20% yield. Lindlar reduction (H_2/Pd-$BaSO_4$, quinoline) of 5 followed by reduction with LAH provided β-dienol

(7) (mp 115°C) in 56% yield. The stereochemistry of compound (7) was assigned on the basis of ^{1}H-nmr decoupling.[5]



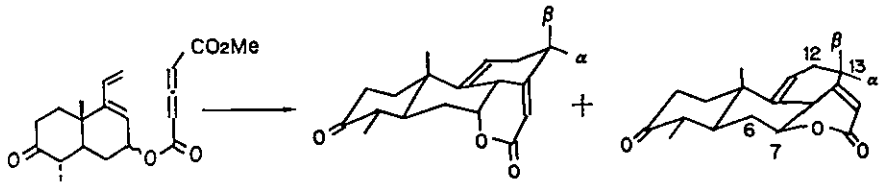
Scheme I. Reagents and conditions: i, LiC≡CH, THF, -78° C(3 days); ii, $POCl_3$/DBU, CH_2Cl_2; iii, DBU, 140° C(3 h); iv, CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2; v, H_2, Pd-$BaSO_4$, quinoline; vi, LAH, THF, 0° C;



Scheme II. Reagents and conditions: i, PhSeCl/LDA, -78° C, H_2O_2/pyridine; ii, LiC≡CH, THF, -78° C(3 days); iii, 25% H_2SO_4, diethyl ether, room temperature; iv, DCC, pyridine, CH_2Cl_2, room temperature(23 h); v, Et_3N, THF, 0° C(48 h)

We further examined alternative efficient synthetic routes to the dienol (Scheme II). The enone (8) obtained by dehydrogenation of 1 was converted to 9 with the ethylenediamine complex of lithium acetylide in 80% yield. The acetylenic alcohol (9) could be rearranged to a 2:1 mixture of 11ax and 11eq by treatment with 25% H_2SO_4 in diethyl ether in 32% yield.[4] Lindlar reduction of the 11ax/11eq mixture afforded a mixture of dienols (12ax)/(12eq) in near quantitative yield. Esterification (DCC/pyr, yield 64%) of the mixture 12ax/12eq with the half ester (13)[7] followed by allenylation provided a mixture of allene-1,3-dicarboxylates (15ax)/(15eq) in near quantitative yield.

Heating of the mixture of allenes (15ax)/(15eq) in o-xylene for 3 h at 145°C gave the [4+2] cycloadducts (16) (yield 29%) and (17) (17%) as each an epimeric mixture [1:1 in 16, 2:1 in 17] (Scheme III). Fortunately, each recrystallization from iso-propyl ether of 16 and 17 afforded the single isomers 16α and 17α, respectively. The structural assignment of these compounds was accomplished by the spectral inspection. Mass spectra of these adducts showed molecular ion peaks at m/z 344. Ir spectra exhibited a band characteristic to δ-lactone at 1710 cm^{-1} while their ^1H-nmr spectra showed two olefinic proton signals. The stereochemistry of these adducts was confirmed by J values observed between the protons on C_6 and C_7, and C_{12} and C_{13}, respectively.[8]



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16α : α=CO2Me, β=H
16β : α=H, β=CO2Me

17α : α=CO2Me, β=H
17β : α=H, β=CO2Me

Scheme III. Diels-Alder reaction of allenes (15). Condition: o-xylene, 145° C(3 h)

The intramolecular Diels-Alder reaction of allene-1,3-dicarboxylates provided the quassin basic skeleton, tetracyclic lactones represents useful tool to construct bruceantin basic skeleton which continues to occupy the attention of synthetic organic chemists worldwide.

REFERENCES

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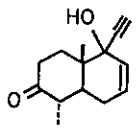
2. P.A. Grieco, S. Ferrino, and G. Vidari, J. Am. Chem. Soc.,1980, 102, 7586.
3. F. Kuo and P.L. Fuchs, J. Am. Chem. Soc., 1987, 109, 1122 and references cited therein.
4. M. Yoshida, M. Hiromatsu, and K. Kanematsu, J. Chem. Soc., Chem. Commun., 1986 1168.
5. The hydroxyl group was confirmed to be β-equatorial by J value (13.8 Hz) observed between the protons on C_6 and C_7.
6. Although the isolated yield for 11 is only moderate, this is mainly due to the relatively low conversion of the reaction, and the reaction itself is clean. Namely, substantial amounts of deprotected starting acetylenic alcohol (10) was recovered, which could be repeated the same reaction.



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7. C. P. Dell and E. H. Smith, J. Chem. Soc., Perkin Trans. 1. 1985, 747.
8. 16α: mp 176-178° C, ^{1}H-nmr ($CDCl_3$) δ 5.94(d, 1H, J=1.3Hz, $C_{13}H$) 5.47(m, 1H, $C_{11}H$) 4.74(m, 1H, C_7H) 3.76(s, 3H, $COOCH_3$) 3.60(dm, 1H, J=7.2Hz, $C_{13}H$) 3.48(m, 1H, C_8H) 2.87(ddm, 1H, J=18, 4.7Hz, $C_{12}Heq$) 2.6-1.5(m, 9H) 1.28(s, 3H, $C_{15}H_3$) 1.07(d, 3H, J=6.4Hz, $C_{16}H_3$)

   17α: mp 186-188° C, ^{1}H-nmr ($CDCl_3$) δ 5.93(d, 1H, J=1.1Hz, $C_{13}H$) 5.54(dd, 1H, J=6.6, 3.3Hz, $C_{11}H$) 4.89(ddm, 1H, J=10, 6Hz, C_7H) 3.76(s, 3H, $COOCH_3$) 3.59(dd, 1H, J=7.9, 1Hz, $C_{13}H$) 3.29(m,1H, C_8H) 2.94(dm, 1H, J=18Hz, $C_{12}Heq$) 2.6-1.6(m, 9H) 1.31(s, 3H, $C_{15}H_3$) 1.05(d, 3H, J=6.6Hz, $C_{16}H_3$)

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