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AN INTRAMOLECULAR DIELS-ALDER APPROACH TO QUASSINOIDS——A STEREOSELECTIVE CONSTRUCTION OF A-AROMATIC KLAINEANONE

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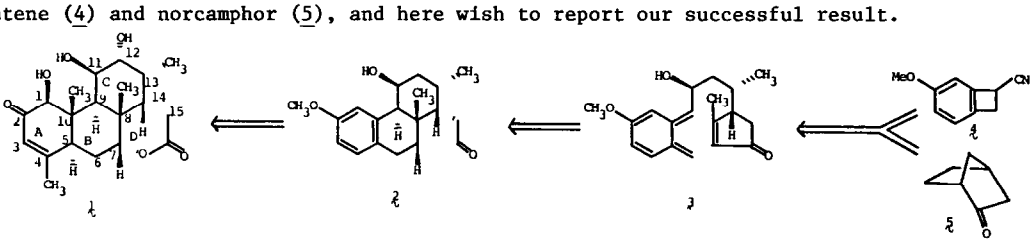
Summary Thermolysis of a benzocyclobutene derivative (20) prepared from norcamphor produced stereoselectively a tetracyclic compound (2), which was converted to a lactone (21) having correct stereochemistry at C_7, C_8, C_9, C_{11}, C_{13}, and C_{14} positions of (±)-klaineanone.

Quassinoids are highly oxygenated degraded triterpenes found in plants of Simaroubaceae.[1] Recent extensive work on this group is mainly attributed to the potent antileukemic activity of the C_{15}-acyloxylated derivatives such as bruceantin, reported by Kupchan et al.[2] Furthermore the oxygen functionality present in quassinoids coupled with its complicated stereostructure has stimulated a great deal of synthetic activity. Recently Grieco and coworkers elegantly synthesized (±)-quassin by employing intermolecular Diels-Alder strategy.[3] We had investigated synthesis of this type of terpene by thermolysis of benzocyclobutene derivatives.[4,5] In further continuation of this study, we envisioned a stereoselective construction of a tetracyclic compound (2), possessing the same B,C,D-ring fusion as that of the natural quassinoid, e.g. klaineanone (1),[6] by intramolecular Diels-Alder reaction[7] of an o-quinodimethane (3) derived from a benzocyclobutene (4) and norcamphor (5), and here wish to report our successful result.

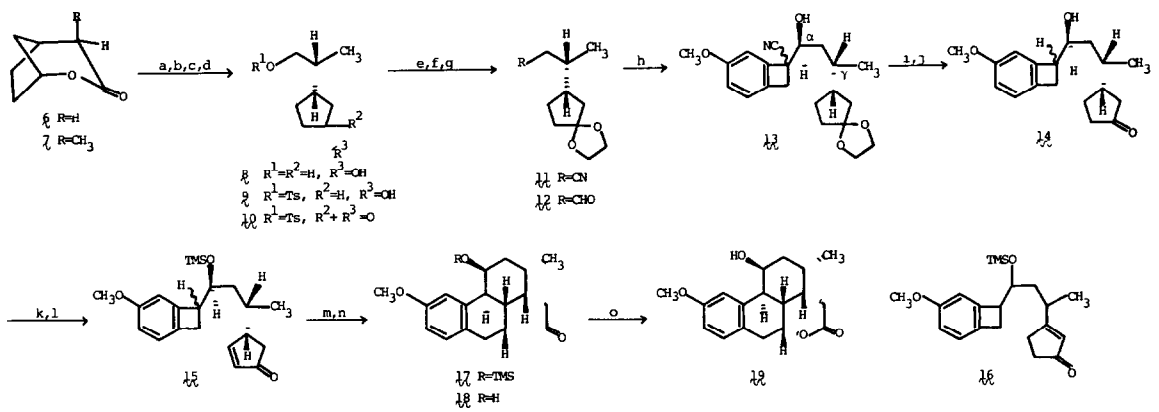


Methylation of the lactone (6),[8] prepared from norcamphor, produced exclusively one stereoisomer (7),[9] whose stereostructure was assigned from the consideration of an approach of methyl iodide to the enolate anion from less hindered side. Thus the relative configuration between C_{13} and C_{14} positions of klaineanone (1) was arranged in this molecule. After reduction of (7) with lithium aluminum hydride, the primary alcohol of the resulting diol (8)[9] was selectively tosylated to (9),[9] which was then oxidized to the ketone (10),[9] mp 60°, with Jones reagent. Protection of the ketone (10) followed by cyanation gave the nitrile (11),[9] which was converted, on diisobutylaluminum hydride reduction and successive hydrolysis, to the aldehyde (12).[9] Aldol condensation of (12) with the benzocyclobutene (4)[10] was conducted in the presence of sodium amide in liquid ammonia to afford the alcohol (13)[9] as a stereoisomeric mixture. The stereochemical

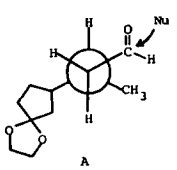
relationship between α and γ positions of side chain of the main constituent of the benzocyclobutene (13) was assumed by examination of a Dreiding model, namely the benzocyclobutenyl anion would close to the aldehyde group as shown in A. This assignment was confirmed by X-ray analysis of the derivative (19) (vide infra).

The unnecessary cyano group had been removed by treatment with sodium in liquid ammonia[11] before deprotection of the ketal group. The desired alcohol (14)[9] was obtained in 56.7 % yield from the aldehyde (12) along with the corresponding dehydroxylated compound[4] (17.8 %). Formation of silyl enol ether from (14), followed by dehydrogenation with palladium acetate in the presence of p-benzoquinone[12] yielded, after column chromatography on silica gel, the enone (15)[9] (48.6 %) [IR ($CHCl_3$) 1720 cm^{-1}; NMR ($CDCl_3$) δ 6 18 (1H, dd, J = 2 and 6 Hz), 7.66 (1H, dd, J = 3 and 6 Hz), MS m/e 358 (M^+)], the isomer (16)[9] (11.2 %), and the silyl enol ether intermediate (11 %) which could be reused for the oxidation.

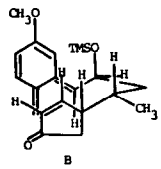
As a model experiment, the intramolecular Diels-Alder reaction was examined utilizing the above enone (15). Heating a solution of (15) in o-dichlorobenzene at 230°C for 2.5 h in sealed tube produced a tetracyclic compound (17) in 81 % yield. It is considered that endo forms during the cycloaddition would be unfavored because of serious interaction between aromatic ring and methyl group or hydrogens. One (B) of the two exo-modes would be a prefered conformation and form the BC(trans), BD(cis), and CD(cis) fused product (17), while other conformations would have heavy nonbonding interaction between the diene and the allylic hydrogen. The expected relative configuration was suggested from NMR spectrum of the desilylated compound (18),[9] mp 184° [IR ($CHCl_3$) 1740 cm^{-1}, MS m/e 286 (M^+)], in which the methine hydrogen present at the C_{11} position was observed at a low field, 4.66 ppm due to the deshielded effect of the benzene ring.



(a) LDA, THF, -78°C MeI, -78°C, 1 h -20°C, 2 h (77 %) (b) LAH, THF, 0°C, 2 h (82 %) (c) TsCl, pyridine, 0°C, 45 min (51 %) (d) CrO_3, H_2SO_4, acetone, r t , 2 h (74 %) (e) TsOH, $HOCH_2CH_2OH$, benzene, reflux, 3 h (f) KCN, DMF, 70°C, 4 h (94 % from 10) (g) DIBAL, toluene, -78°C, 2 h r t , 2 h (72 5 %) (h) 4, $NaNH_2$, NH_3, -78°C, 1 5 h (i) Na, NH_3-THF, -78°C, 30 min (j) 3 % HCl, MeOH, r t , 2 h (56 7 % from 12) (k) LDA, THF, -78°C TMSCl, -78°C, 1 h 0°C, 1 h (l) $Pd(OAc)_2$, p-benzoquinone, CH_3CN, r t , 18 h (48 6 % form 14) (m) o-dichlorobenzene, 230°C, 2 5 h (81 %) (n) 2 % HCl, CH_2Cl_2-MeOH, 0°C, 1 h (80 %) (o) MCPBA, TsOH, CH_2Cl_2, r t , 5 h (47 %)

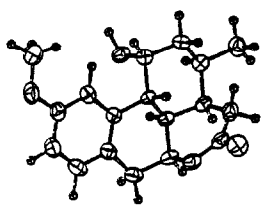


A



B

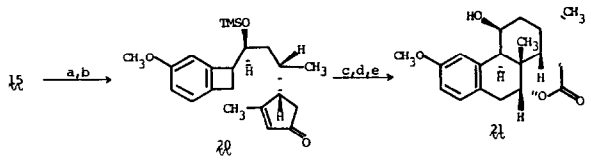
Baeyer-Villiger oxidation migrating the tertiary carbon of (18) was achieved by the action of m-chloroperbenzoic acid in the presence of p-toluenesulfonic acid. The stereochemistry of the resulting lactone (19),[9] mp 218° [IR ($CHCl_3$) 1720 cm^{-1}; MS m/e 302 (M^+)] was unambiguously established by its X-ray analysis.[13] It is now made clear that the relative stereochemistry at all six chiral centers of (19) is identical with that of klaineanone (1) as expected.



Molecular Structure of One of Enantiomers of the Tetracyclic Lactone (19)

Introduction of methyl group to the above enone (15) was accomplished by conjugate addition using dimethylcopperlithium followed by quenching with trimethylsilyl chloride[14] and subsequent oxidation with palladium acetate.[12] Thermolysis of the benzocyclobutene (20),[9] [IR ($CHCl_3$) 1680 cm^{-1}, MS m/e 372 (M^+)] and deblocking furnished in 57.0 % yield the tetracyclic ketone (2),[9] mp 161° [IR ($CHCl_3$) 1740 cm^{-1}, MS m/e 300 (M^+)], which was converted into the lactone (21),[9] mp 114° [IR ($CHCl_3$) 1725 cm^{-1}; NMR δ 0.94 (3H, d, J = 7 Hz), 1.16 (3H, s), 3.77 (3H, s), 4.20 (1H, dd, J = 2 and 4 Hz), 4.72 - 4.92 (1H, m), MS m/e 316 (M^+)] under the foregoing conditions The stereochemistry of these products (2 and 21) was determined by the spectral comparison with the 8-nor-compounds.

Thus an efficient and stereoselective route to A-aromatic klaineanone was developed through intramolecular Diels-Alder approach. Further transformation of the tetracyclic lactone to quassinoids is in progress.



(a) Me_2LiCu, Et_2O, 0°C, 0 5 h, TMSCl, Et_3N, HMPA, r t , 2 h (b) $Pd(OAc)_2$, p-benzoquinone, CH_3CN, 40°C, 5 h(47 % from 15) (c) o-dichlorobenzene, 210~220°C, 3 h (d) 10% HCl, $^nBu_4NBr$, CH_2Cl_2-MeOH, reflux, 20 h (57 % from 20) (e) MCPBA, TsOH, CH_2Cl_2, r t , 14 h (24 %)

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(9) All new compounds have been fully characterized by IR ($CHCl_3$), NMR ($CDCl_3$), and mass spectra and elemental analysis. (7): IR 1720 cm^{-1} (C=O); NMR δ 1.27 (3H, d, J = 7 Hz, Me), 4.70 (1H, br s, CHOCO). (8): NMR δ 0.97 (3H, d, J = 7 Hz, Me), 3.40 - 3.67 (2H, m, CH_2OH), 4.20 - 4.43 (1H, m, >CHOH); MS m/e 144 (M^+). (9): NMR δ 0.93 (3H, d, J = 6 Hz, Me), 2.47 (3H, s, ArMe). (10): IR 1740 cm^{-1} (C=O); NMR δ 1.00 (3H, d, J = 7 Hz, Me), 2.47 (3H, s, ArMe), 3.93 (2H, d, J = 5 Hz, CH_2OTs); MS m/e 296 (M^+). (11): IR 2250 cm^{-1} (CN); NMR δ 1.10 (3H, d, J = 6 Hz, Me), 2.20 - 2.42 (2H, m, CH_2CN), 3.87 (4H, s, OCH_2CH_2O), MS m/e 195 (M^+). (12): IR ($CHCl_3$) 1725 cm^{-1} (CHO); NMR δ 0.94 (3H, d, J = 6 Hz, Me), 3.87 (4H, s, OCH_2CH_2O), 9.73 (1H, br s, CHO), MS m/e 199 (M^+ + 1). (13): IR 3575 (OH), 2230 cm^{-1} (CN), NMR δ 0.77 - 1.10 (3H, m, Me), 3.78 (3H, s, OMe), 3.88 (4H, s, OCH_2CH_2O); MS m/e 357 (M^+). (14): IR 3600 (OH), 1740 cm^{-1} (C=O), NMR δ 0.97 (3H, d, J = 6 Hz, Me), 3.70 - 4.00 (1H, m, >CHOH), 3.77 (3H, s, OMe), MS m/e 288 (M^+). (16): NMR δ 0.05 (9H, s, $SiMe_3$), 1.18 (3H, d, J = 7 Hz, Me), 3.80 - 4.10 (1H, m, >CHOTMS), 3.75 (3H, s, OMe), 5.93 (1H, br s, =CHCO); MS m/e 358 (M^+). (18): NMR δ 1.00 (3H, d, J = 7 Hz, Me), 3.77 (3H, s, OMe), 4.66 (1H, br s, >CHOH), 6.69 (1H, dd, J = 2 and 8 Hz, ArH), 6.86 (1H, d, J = 2 Hz, ArH), 7.04 (1H, d, J = 8 Hz, ArH). (19). NMR δ 0.90 (3H, d, J = 7 Hz, Me), 3.78 (3H, s, OMe), 4.90 (2H, br s, C_7-H and C_{11}-H). (20): NMR δ 0.00 (9H, s, $SiMe_3$), 0.93 (3H, d, J = 7 Hz, Me), 2.04 (3H, s, Me), 3.88 - 3.93 (1H, m, >CHOTMS), 3.67 (3H, s, OMe), 5.90 (1H, br s, =CHCO). (2) NMR δ 1.00 (3H, d, J = Hz, Me), 1.12 (3H, s, Me), 3.77 (3H, s, OMe), 4.70 (1H, br s, >CHOH), 6.68 (1H, dd, J = 2 and 8 Hz, ArH), 6.90 (1H, d, J = 2 Hz, ArH), 7.05 (1H, d, J = 8 Hz, ArH).

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(13) Orthorhombic, space group $Pna2_1$ with a = 20.511(2), b = 5.153(1), c = 14.332(2) Å; D_{calc} = 1.326 g/cm^3 for Z = 4. Final R value was 0.045 for 1168 observed reflections.

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