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Norbornyl Route to Polyoxygenated Cyclohexanes. An Approach to Pancratistatin and Narciclasine Alkaloids

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Abstract: A stereoselective approach to densely functionalized cyclohexanoids from 7-norbornenone is delineated. Construction of the phenanthridone core present in pancratistatin has been accomplished through this protocol.

The readily available bicyclo[2.2.1]heptane (norbornane) framework, with its inherent stereo- and regioselective proclivities, has served as an enduring building block in diverse synthetic endeavors. More commonly, the norbornyl system has been exploited for the synthesis of many cyclopentanoids *e.g.* prostaglandins, through the extraction of either of the two five-membered rings present in its bridged bicyclic structure.[1] However, the serviceability of the norbornyl framework as a potentially rich repository of stereo- and regiochemically well-defined six-membered ring compounds, has received only limited attention.[2] In this, and the accompanying communication, we demonstrate the versatility of the 7-ketonorbornyl derivatives in readily furnishing a range of functionally and stereochemically embellished cyclohexane derivatives that are well poised for application to the synthesis of a variety of interesting natural products.

Readily available *endo*-phenyl-7-norbornenone-dimethyl acetal **1**,[3] on stereoselective dihydroxylation from the *exo*-face and exposure to amberlyst-15 in acetone underwent the desired deprotection-protection to furnish the acetonide **2**in excellent yield. Baeyer-Villiger oxidation of **2** led to a mixture of regioisomeric lactones (85:15) which as such on LAH reduction furnished the diols **3** (major) and **4** (minor), respectively. Acetonide deprotection in **3** and **4** and acylation furnished the tetraacetates **5**[4] and **6**,[4] respectively, in a short efficient sequence from **1**, Scheme 1. In another set of reactions, **1** was subjected to deketalization to yield *endo*-phenyl-7-norbornenone **7** and further Baeyer-Villger oxidation led to a regioisomeric mixture of lactones (40:60). LAH reduction of lactones furnished the diols **8** (minor) and **9** (major), respectively. Dihydroxylation of the diols **8** and **9** with OsO_4 proceeded with complete diastereoselectivity, according to the predictions of Kishi *et al.*,[5] and after acylation tetraacetates **10**[4] and **11**[4] were obtained, Scheme 1.

Thus, pentasubstituted cyclohexanoids **5**, **6**, **10** and **11** of fully secured stereochemistry and well-defined substitution pattern became readily accessible from a single precursor **1**, in just a few steps. It is noteworthy that, by simply reversing the sequence of dihydroxylation and Baeyer-Villger oxidation from **1**, the stereochemistry in the products **5**, **6**, **10** and **11** can be controlled. It is also worth

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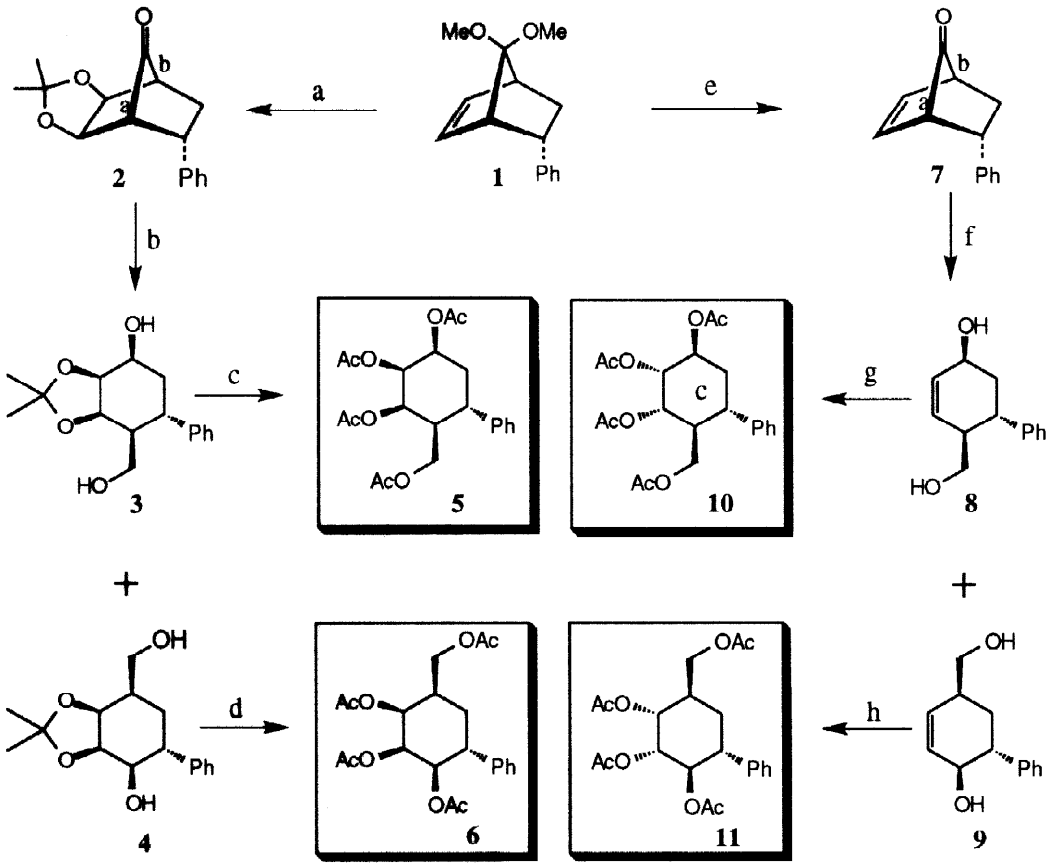
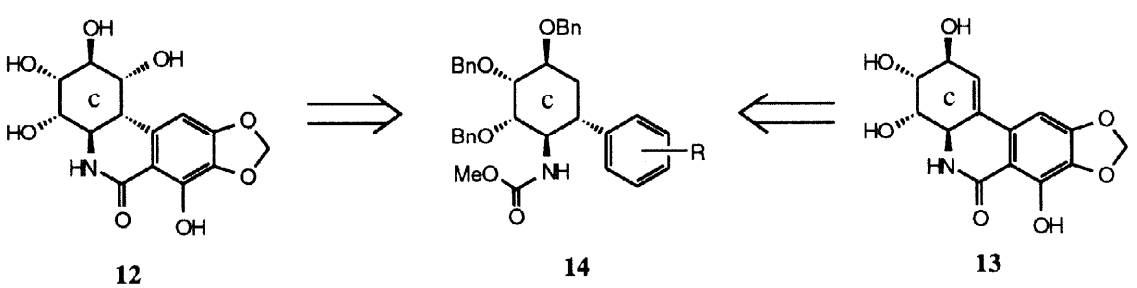
noting that the regioselectivity of Baeyer-Villger oxidation in **2** (85:15, preferred migration of bond 'b') is significantly different from **7** (40:60, preferred migration of bond 'a').[6]

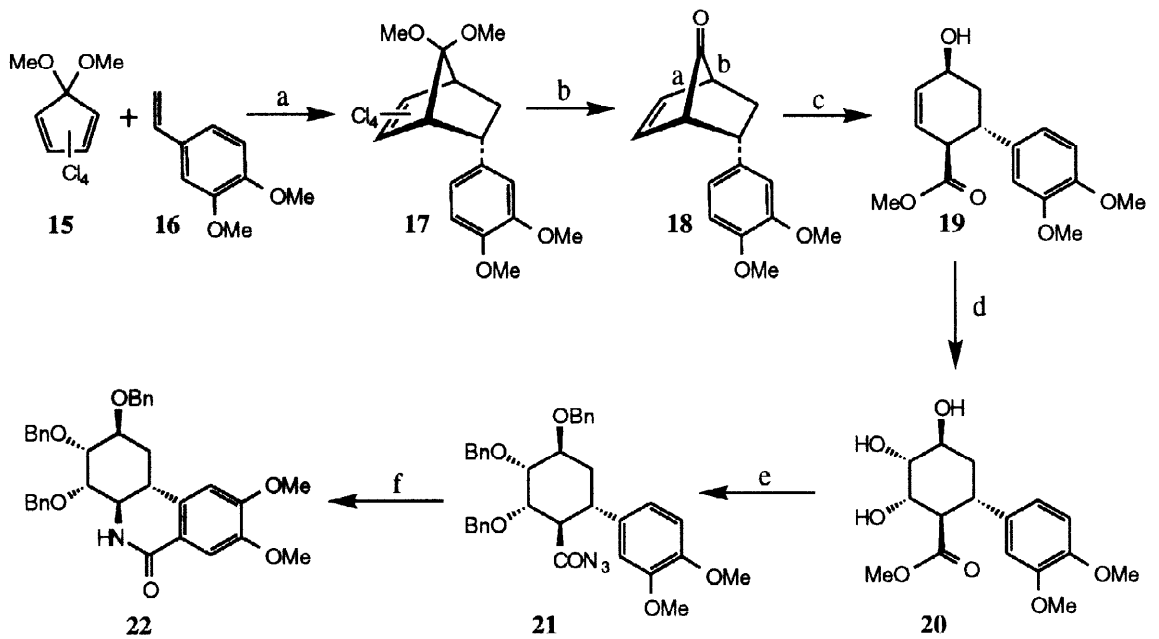


Scheme 1. Reagents and Conditions: (a) i. OsO_4, NMMO, aq.Me_2CO, 55%; ii. Amberlyst-15, Me_2CO, 90%; (b) MCPBA, 0-5°C, DCM, 90%; LAH, THF, -18°C→rt, 68% for **3** & 12% for **4** (isolated); (c) Amberlyst-15, MeOH; Ac_2O, Py, 55%; (d) Amberlyst-15, MeOH; Ac_2O, Py, 82%; (e) Amberlyst-15, Me_2CO, Δ, ~85%; (f) H_2O_2 (30%), AcOH, 35-40%; LAH, THF, 0-5°C, 32% for **8** & 44% for **9** (isolated); (g) i. OsO_4, NMMO, aq.Me_2CO, 95%; ii. Ac_2O, Py, ~70%; (h) i. OsO_4, NMMO, aq. Me_2CO, 76%; ii. Ac_2O, Py, 78%.



The substitution and stereochemical pattern present in **10** (*cf.* **14**) was reminiscent of the ring-C of biologically active alkaloids of pancratistatin **12** and narciclasine-type **13** of contemporary interest.[7] Indeed, compounds related to **14** have served as the advanced precursors of **12** and **13** in several synthetic approaches. We, therefore, ventured to adapt our route to **10** towards the construction of the tricyclic core present in natural products **12** and **13**.

Diels-Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **15** and the 3,4-dimethoxystyrene **16** furnished the *endo*-adduct **17**, which on reductive dechlorination and deketalization led to the *endo*-aryl-7-norbornenone **18**.[4] Baeyer-Villiger oxidation furnished a regioisomeric mixture of lactones (30:70, preferred migration of bond 'a'), which as such was hydrolyzed and esterified to furnish the corresponding allylic alcohols. Dihydoxylation of the minor alcohol **19**[4] proceeded with predicted diastereoselectivity[4] to furnish the trihydroxy ester **20**[4]. After the protection of the hydroxyl functionalities in **20**, the ester moiety was elaborated to give acylazide **21**.[4] Curtius rearrangement sequence from **21** led to the intermediate carbamate, which further cyclized to give the phenanthridone **22**[4] having the tricyclic framework and ring-C substitution pattern present in **12** and **13**, Scheme 2.



Scheme 2. Reagents and Conditions: (a) Δ, 84%; (b) i. Na, NH_3, -78°C, 72%; ii. Amberlyst-15, Me_2CO, Δ, 85%; (c) i. H_2O_2 (30%), AcOH, 55%; ii. NaOH, aq. THF and then CH_2N_2, Et_2O, 23% for **19**& 55% (isolated) for the other regioisomer. (d) OsO_4, NMMO, aq. Me_2CO, ~80%;(e) i. BnBr, NaH, 91%; ii. 20%KOH-MeOH, Δ, ~70%; iii. $(COCl)_2$, Py, DCM, 0°C; NaN_3, Me_2CO, 91%; (f) i. Xylene, Δ; MeOH, Δ, 50%; iii. $POCl_3$, sealed-tube, ~80°C, <10%.

In summary, we have outlined a short, simple approach of general utility to highly functionalized cyclohexanoids from readily available starting materials and demonstrated its efficacy in constructing the tricyclic core of pancratistatin and narciclasine.[7,8]

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4. **All new compounds were duly characterized (IR, ^1H & ^{13}C NMR at 200 and 50 MHz, respectively in $CDCl_3$, MS). Selected spectral data:**
5: δ_H **7.36-7.18 (5H, m, Ar-H), 5.58 (1H, dd as t, J=2.6Hz),** 5.40 (1H, dd, J=5.8, **3.1Hz), 5.06 (1H, dd, J=3.8, 3.1Hz), 3.95 (1H,dd as t, J=~11Hz),** 3.55 (1H, dd, J=11, 4.8Hz), 3.03 **(1H, td, J=12, 4Hz), 2.47-2.32 (1H, m), 2.15 (3H, s), 2.14** (3H, s), 2.08-1.82 (2H, m), 2.02 (3H, s), 1.93 **(3H, s)**; δ_C 170.75, 170.07(2C), 169.96, 141.45, 129.04(2C), 127.31(2C), 127.18, 70.35, 68.32, 67.28, 62.07, 42.90, 37.36, 35.85, 21.09, 20.77, 20.68(2C). **6**: δ_H 7.31-7.19 (5H, m, Ar-H), 5.56 (1H, dd as t, J=2.76Hz), 5.21 (1H, dd as t, J=2.6Hz), 5.17 (1H, dd as t, J=2.9Hz), 4.58-4.47 (1H, m), 4.36 (1H, dd, J=12, 4Hz), 3.22 (1H, td, J=12, 4Hz), 2.51-2.46 (1H, m), 2.19 (3H, s), 2.14-2.06 (2H, m), 2.08 (3H, s), 2.04 (3H, s), 1.77 (3H, s); δ_C 171.14, 169.89, 169.66(2C), 140.06, 128.61(2C), 127.51(2C), 127.11, 72.36, 70.24, 69.90, 62.17, 37.79, 36.70, 30.87, 20.99(2C), 20.82, 20.45. **10**: δ_H 7.36-7.18 (5H, m, Ar-H), 5.39-5.29 (1H, m), 5.27 (1H, dd, J=11.3, 3.0Hz), 5.11-5.08 (1H, m), 4.14 (1H, dd, J=11.6, 2.5Hz), 3.52 (1H, dd, J=11.6, 2.5Hz), 3.03 (1H, td, J=12, 4Hz), 2.40-2.27 (2H, m), 2.19 (6H, s), 2.11-1.98 (1H, m), 2.01 (3H, s), 2.00 (3H, s); δ_C 170.63, 169.95, 169.35, 169.54, 141.75, 128.86(2C), 127.54(2C), 127.18, 69.40, 68.67, 68.29, 60.58, 40.64, 38.90, 33.20, 21.09, 20.89, 20.70(2C). **11**: δ_H 7.30-7.22 (5H, m, Ar-H), 5.58-5.48 (2H, m), 5.12 (1H, dd, J=9.8, 3.06Hz), 4.38-4.19 (2H,m), 3.09-2.93 (1H, m), 2.42-2.20 (2H, m), 2.18(3H, s), 2.11 (3H, s), 1.95 (3H, s), 1.85-1.75 (1H, m), 1.75 (3H, s); δ_C 170.65, 169.98, 169.83, 169.46, 140.08, 128.47(2C), 127.66(2C), 127.17, 72.51, 71.41, 70.40, 63.22, 43.63, 37.73, 29.32, 20.96, 20.69, 20.53, 20.38. **18**: δ_H 6.79-6.60 (4H, m), 6.28 (1H, dd, J=6.77, 3.46Hz), 3.84 (3H, s, OMe), 3.83 (3H, s, OMe), 3.54-3.44 (1H, m), 3.13 (1H, t, J=4Hz), 2.99 (1H, t, J=4Hz), 2.54-2.41 (1H, m), 1.52 (1H, dd, J=12.3, 6.1Hz); δ_C 204.26, 148.82, 147.96, 135.14, 133.50, 130.37, 120.08, 111.92, 111.17, 55.94(2C), 53.13, 47.24, 37.75, 30.85; *m/z* 244 (M^+). **21**: δ_H 7.34 (15H, br s, Ar-H), 6.79-6.72 (3H, m, Ar-H), 4.81-4.41 (6H, m), 4.27-4.11 (1H, m), 3.94-3.90 (2H, m), 3.87 (3H, s), 3.86 (3H, s), 3.73-3.70 (1H, m), 3.08-2.94 (1H, m), 2.09-1.92 (2H, m); δ_C 155.87, 149.06, 147.91, 138.68, 138.41, 134.68, 128.38, 127.98, 127.78, 127.46, 119.69, 111.16, 78.57, 75.19, 74.47, 73.11, 72.05, 71.14, 56.01, 55.89, 55.10, 42.13, 33.45. **22**: δ_H 7.62 (1H, s), 7.36-7.28 (15H, m), 6.67 (1H, s), 6.21 (1H, s, D_2O exchange), 4.73-4.43 (7H, series of m), 3.93 (6H, s, OMe), 3.87-3.81 (3H, m), 3.20-3.12 (1H, m), 2.39-2.31 (2H, m); FABMS *m/z* 579 (M^+).

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