C_{19} quassinoid model studies: Preparation of *trans*-perhydroindans via a vinylogous Mukaiyama aldol – free-radical cyclization route[1]

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Abstract: Aldehyde **9** was prepared in 5 steps from 3,5-dimethylbenzoic acid. Treatment of **9** with ketene acetals **10** and **19** and titanium tetrachloride gave free-radical cyclization substrates **11** and **20** in 67% and 51% yields, respectively. Tri-*n*-butylstannane-mediated cyclization of **11** and **20** gave *trans*-perhydroindans **14** and **21** in 60% and 63% yields, respectively. The relationship of these studies to an approach to C_{19} quassinoids is discussed.

Key words: vinylogous Mukaiyama aldol reaction, free-radical cyclization, *trans*-perhydroindans, C_{19} quassinoids, 1,2-asymmetric induction.

Résumé : L'aldéhyde **9** est préparé en 5 étapes à partir de l'acide 3,5-diméthylbenzoique. Le traitement de **9** avec les acetals de kétène **10** et **19** et le tetrachlorure de titane donne les substrats de cyclisation par radicaux libres **11** et **20** avec des rendements respectifs de 67% et 51%. La cyclisation de **11** et **20** par le tri-*n*-butylstanne donne les *trans*-perhydroindanes **14** et **21** avec des rendements respectifs de 60% et 63%. On discute la relation de ces études avec une approche vers les quassinoides en C_{19}.

Mots clés : réaction d'aldol vinylogue de Mukaiyama, cyclisation par radicaux libres, *trans*-perhydroindanes, quassinoides en C_{19}, induction asymétrique-1,2.

Introduction

The C_{19} quassinoids are a small family of terpenoids that have received less attention from the synthetic community than the corresponding C_{20} quassinoids (1). Indeed only the second synthesis of a C_{19} quassinoid was reported in 1999, when Grieco described a synthesis of (5*R*)-polyandrane (**1**) (2). We have been investigating a unified approach to selected C_{19} and C_{20} quassinoids that involves an extension of free-radical cyclization chemistry previously developed in our laboratories (3). The plan for the polyandranes (Fig. 1) involves preparation of *trans*-perhydroindans of type **2** via free-radical cyclization of substrates of type **3**. This communication reports preliminary results of this study.

Results and discussion

Our first objective was to prepare a substrate of type **3** where the incipient C_{11} hydroxyl group of the polyandranes is replaced with a methyl group and R_1 and R_2 are electron-withdrawing and methyl groups, respectively. The specific substrate selected for synthesis (**11**) was prepared as described in Schemes 1 and 2. 3,5-Dimethylbenzoic acid (**4**) was subjected to Birch reduction, according to an established procedure, to provide **5** (mp 113–115 °C) in 95% yield (4). Aldol condensation of the dianion derived from **5** with formaldehyde provided hydroxy acid **6** in 93% yield (5). Reduction of **6** using lithium aluminum hydride provided diol **7** (mp 99 to 100 °C) in 57% yield. Treatment of **7** with NBS in tetrahydrofuran gave cycloetherification product **8** (99%), and oxidation of the primary alcohol using Swern's conditions provided aldehyde **9** in 96% yield (6).

Reaction of **9** with dienol ether **10** (7) in the presence of titanium tetrachloride gave a 6:1 mixture of vinylogous Mukaiyama aldol products **11** (67%) and **12** (11%) (8).[3] We note that promotion of the vinylogous Mukaiyama aldol with boron trifluoride etherate provided **11** (mp 134 to 135 °C) and **12** (mp 83–85 °C) in 11% and 42% yields, respectively.

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Dedicated to Professor Edward Piers whose commitment to science and education is admirable.

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[1]This article is part of a Special Issue dedicated to Professor Ed Piers.
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[3]The stereochemical assignments at C_7 for **11** and **12** were based on NMR correlations with related compounds, including one for which an X-ray crystal structure was obtained. NMR studies on the cyclization products derived from **11** and **12** also clearly defined C_7 stereochemistry.

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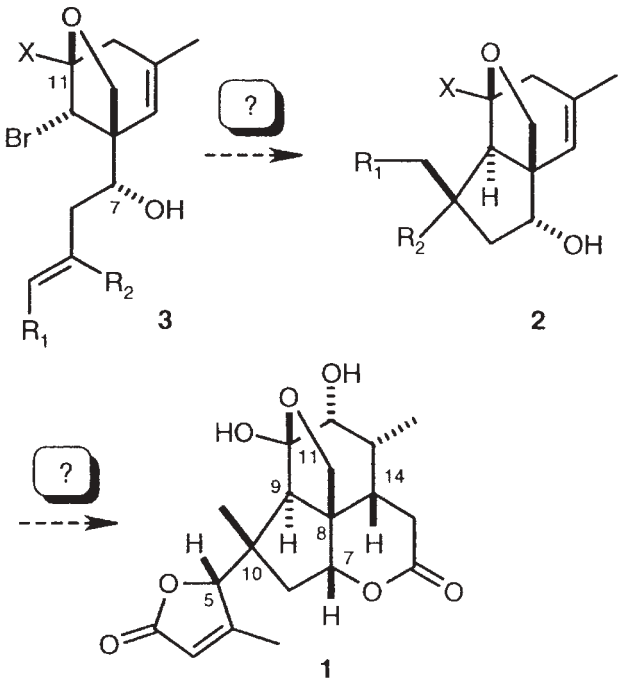
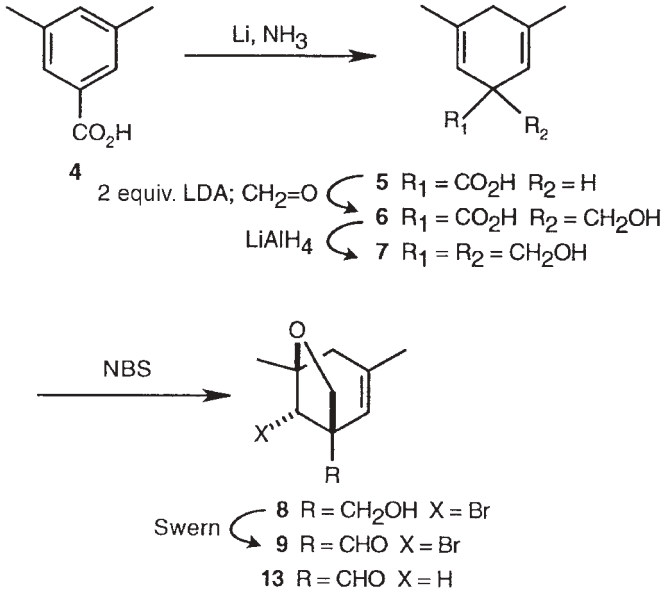
Fig. 1. Synthetic plan.

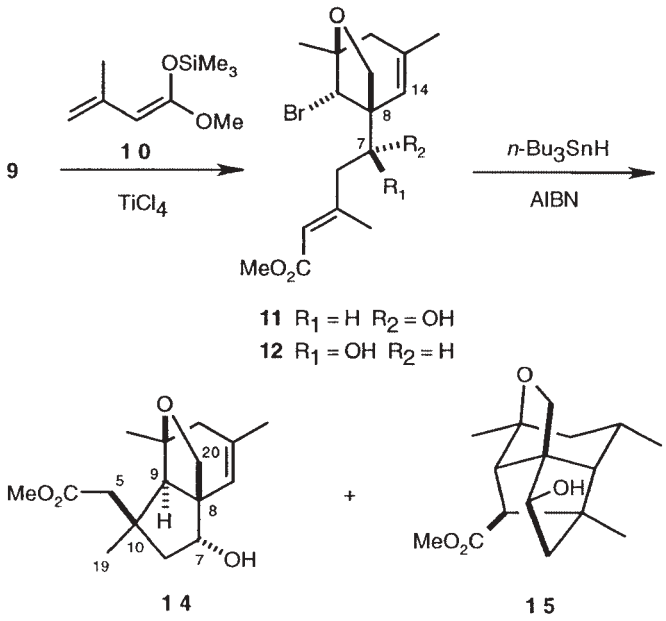


Scheme 1. Synthesis of aldehyde **9**.



In addition, titanium tetrachloride mediated reaction of *des*-bromo compound **13** with **10** gave a complex mixture of products that contained very little material resulting from a vinylogous aldol. Thus, the nature of the Lewis acid and the presence of a bromine atom in **9** play a central role in the observed diastereoselectivity. We speculate that the stereoselectivity observed with titanium tetrachloride is due to a combination of a chelation effect and principles for 1,2-asymmetric induction introduced by Felkin and co-workers

Scheme 2. Vinylogous Mukaiyama aldol – free-radical cyclization.



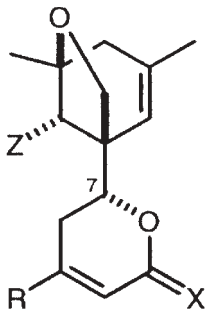
(9*a*) and Ahn and Eisenstein (9*b*). Thus, a complex between the Lewis acid and **9**, which involves bridging of the bromine and carbonyl oxygen with titanium, is conformationally constrained such that attack *anti* to the C_8—C_{14} bond should be stereoelectronically preferred, giving rise to **11** in a conformation in which substituents are staggered along the C_7—C_8 bond.

Treatment of **11** with tri-*n*-butylstannane in the presence of 2,2′-azobisisobutyronitrile (AIBN) provided cyclization products **14** (60%) and small amounts (less than 6%) of material suspected to be the C_{10} epimer of **14**. We note that a less than 1% yield of **15**, an interesting product derived from an initial 6-endo cyclization, was also isolated. The stereochemistry of **14** was established by difference NOE experiments, which confirmed a *cis*-relationship between the C_7 hydrogen and C_{20} methylene group, a *cis*-relationship between the C_{20} and C_5 methylene groups, and a *cis*-relationship between the C_9 hydrogen and C_{19} methyl group. This result established the viability of the proposed preparation of compounds of type **2** by free-radical cyclization of compounds of type **3**. It also demonstrated that this approach was unlikely to directly afford the required C_9–C_{10} stereochemical relationship.[4]

Two attempts to address the C_9–C_{10} stereochemical problem are described in Fig. 2 and Scheme 3. An examination of molecular models suggested that lactone **17** was constrained such that cyclization would provide the desired C_9–C_{10} stereochemistry. Treatment of **9** with 3-methyl-1-trimethylsiloxy-1,3-butadiene in the presence of potassium *tert*-butoxide followed by Jones oxidation of the resulting lactols **16** provided **17** in 33% overall yield (Fig. 2) (10). We were disappointed to find that attempts to cyclize **17** under a variety of conditions failed (11). For example, typical tri-*n*-

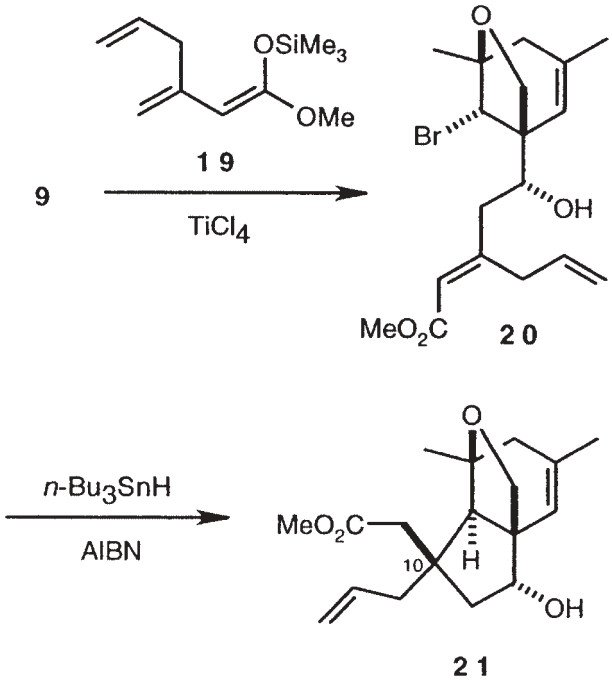
[4] Similar cyclization of **12** provided a 76% yield of the C_7 epimer. We note that derivatives of **11** and **12** lacking the impending C_{10} methyl group were prepared and cyclized with comparable results. In these cases compounds of type **14** (53%–72%) and the corresponding C_{10} epimer (15%–18%) were isolated, and the structures of all products were rigorously established.

Fig. 2. Lactone substrates and products.



16 X = H, OH Z = Br R = Me
17 X = O Z = Br R = Me
18 X = O Z = H R = Me
22 X = O Z = Br R = $CH_2CH{=}CH_2$

Scheme 3. Synthesis and cyclization of **20**.



butylstannane conditions gave only reduction product **18** (mp 135 to 136 °C). Apparently, conformational constraints present in **17** severely retard radical cyclization rates relative to **11**. A potentially useful modification of the chemistry involved cyclization of **20**. This substrate was prepared in 51% yield by reaction of ketene acetal **19** with aldehyde **9** (12).[5,6] Free-radical cyclization of **20** provided **21** in 63% yield. We imagine the reductive decarboxylation of **21** will afford the required C_{10} methyl group.

Characterization data for compounds in synthesis of 21

^{13}C NMR multiplicities in parentheses determined by DEPT spectroscopy.

Hydroxy acid 6

mp 107–110 °C. IR (thin film) (cm^{-1}): 3334, 1707, 1694. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.73 (s, 6H), 2.47, 2.51 (AB q, J = 22.2 Hz, 2H), 3.61 (s, 2H), 5.43 (s, 2H); neither the acidic nor the alcoholic proton were recorded. ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.4 (q), 36.5 (t), 53.2 (s), 69.1 (t), 118.3 (d), 136.5 (s), 179.8 (s). Exact mass calcd. for $C_{10}H_{14}O_3$ ($[M + Na]^+$) m/z: 205.0835; found: 205.0841. Anal. calcd. for $C_{10}H_{14}O_3$: C 65.90, H 7.75; found: C 65.84, H 7.73.

Diol 7

mp 99 to 100 °C. IR (thin film) (cm^{-1}): 3301 (br). ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, J = 6.0 Hz, 2H), 1.69 (s, 6H), 2.43 (s, 2H), 3.37 (d, J = 6.1 Hz, 4H), 5.16 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.5 (q), 37.0 (t), 47.8 (s), 68.8 (t), 121.5 (d), 137.0 (s). Exact mass calcd. for $C_{10}H_{16}O_2$ ($[M + Na]^+$) m/z: 191.1043; found: 191.1045. Anal. calcd. for $C_{10}H_{16}O_2$: C 71.38, H 9.59; found: C 70.88, H 9.47.

Bromo ether 8

mp 49–51 °C. IR (neat) (cm^{-1}): 3419 (br). ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.30 (s, 3H), 1.53 (s, 1H), 1.63 (s, 3H), 2.02 (d, J = 18.1 Hz, 1H), 2.34 (d, J = 18.1 Hz, 1H), 3.65, 3.67 (AB q, J = 11.2 Hz, 2H), 3.81, 3.90 (AB q, J = 6.8 Hz, 2H), 3.96 (s, 1H), 5.19 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.3 (q), 23.6 (q), 44.3 (t), 50.1 (s), 55.8 (d), 63.0 (t), 76.4 (t), 81.5 (s), 122.8 (d), 135.9 (s). Exact mass calcd. for $C_{10}H_{15}BrO_2$ m/z: 246.0255; found: 246.0285. Anal. calcd. for $C_{10}H_{15}BrO_2$: C 48.74, H 6.14; found: C 48.45, H 6.19.

Aldehyde 9

mp 45–48 °C. IR (neat) (cm^{-1}): 2729, 1729. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.43 (s, 3H), 1.79 (s, 3H), 2.17 (d, J = 18.2 Hz, 1H), 2.45 (d, J = 18.3 Hz, 1H), 4.01, 4.10 (AB q, J = 7.1 Hz, 2H), 4.29 (s, 1H), 5.91 (s, 1H), 9.67 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.9 (q), 21.6 (q), 42.7 (t), 52.0 (d), 58.8 (s), 74.3 (t), 81.2 (s), 117.4 (d), 135.7 (s), 197.4 (d). Exact mass calcd. for $C_{10}H_{13}BrO_2$ ($[M + Na]^+$) m/z: 266.9991; found: 267.0009. Anal. calcd. for $C_{10}H_{13}BrO_2$: C 49.18, H 5.37; found: C 49.02, H 5.42.

Ketene acetal 19

IR (neat) (cm^{-1}): 3078, 1650, 1605. ^1H NMR (C_6D_6, 500 MHz) δ: 0.17 (s, 9H), 3.04 (s, 3H), 3.14 (dd, J = 6.5, 1.2 Hz, 2H), 4.21 (s, 1H), 4.95 (d, J = 2.4 Hz, 1H), 5.05 (dd, J = 10.1, 2.1 Hz, 1H), 5.16 (dd, J = 17.1, 2.0 Hz, 1H), 5.31 (d, J = 2.5 Hz, 1H), 6.05 (dddd, J = 17.1, 10.2, 6.8, 6.6 Hz, 1H). ^{13}C NMR (C_6D_6, 125 MHz) δ: 0.47 (q), 42.4 (t), 54.6

[5] Ketene acetal **19** was prepared by deprotonation and silylation of methyl (*E*)-3-methylhexa-2,5-dienoate (12). The reaction of **9** with **19** also provided 6% of the C_7 diastereomer of **20** and several minor products (perhaps lactones) whose structures have yet to be determined.
[6] We note that reaction of **9** with a 1:1 mixture of **19** and its geometrical isomer provided lactones (stereochemistry at C_7 unknown) as the major products (Fig. 1). Thus, ketene acetal geometry influences the stereochemistry of this vinylogous Mukaiyama aldol.

(q), 80.1 (d), 108.6 (t), 115.2 (t), 138.3 (d), 142.0 (s), 157.8 (s). Exact mass calcd. for $C_{11}H_{20}O_2Si$ ($[M]^+$) *m/z*: 212.1227; found: 212.1222.

Dienone 20

mp 98 to 99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.37 (s, 3H), 1.73 (s, 3H), 1.95 (dd, *J* = 13.7, 11.1 Hz, 1H), 2.10 (d, *J* = 18.1 Hz, 1H), 2.25 (br s, 1H), 2.40 (d, *J* = 18.1 Hz, 1H), 2.66 (d, *J* = 13.9 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.2 Hz, 1H), 3.72 (s, 3H), 3.74 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.80 (d, *J* = 6.6 Hz, 1H), 3.88 (d, *J* = 10.8 Hz, 1H), 4.01 (d, *J* = 6.6 Hz, 1H), 4.24 (s, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 5.18 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.30 (s, 1H), 5.8–5.9 (m, 1H), 5.86 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.5 (q), 23.5 (q), 36.8 (t), 41.1 (t), 44.3 (t), 51.5 (q), 52.3 (s), 56.1 (d), 68.6 (d), 72.4 (t), 81.3 (s), 117.6 (t), 119.4 (d), 122.4 (d), 135.2 (d), 136.7 (s), 157.2 (s), 166.5 (s). Exact mass calcd. for $C_{18}H_{25}BrO_4$ ($[M + Na]^+$) *m/z*: 407.0828; found: 407.0802. Anal. calcd. for $C_{18}H_{25}BrO_4$: C 56.11, H 6.54; found: C 56.20, H 6.58.

Perhydroindan 21

IR (neat) (cm^{-1}): 3441, 3075, 3013, 1732, 1639. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.46 (s, 3H), 1.68 (s, 3H), 1.76 (s, 1H), 1.87 (d, *J* = 15.4 Hz, 1H), 2.13 (d, *J* = 17.8 Hz, 1H), 2.36 (d, *J* = 17.8 Hz, 1H), 2.35 (s, 1H), 2.42 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.55 (dd, *J* = 15.4, 5.0 Hz, 1H), 2.66 (d, *J* = 14.5 Hz, 1H), 2.71 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.88 (d, *J* = 14.5 Hz, 1H), 3.62 (d, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 3.92 (d, *J* = 7.7 Hz, 1H), 4.13 (d, *J* = 4.9 Hz, 1H), 5.17 (d, *J* = 4.2 Hz, 1H), 5.20 (s, 1H), 5.89–5.96 (m, 1H), 5.96 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.2 (q), 23.4 (q), 40.4 (t), 45.3 (s), 47.8 (t), 48.4 (t), 51.7 (q), 52.6 (t), 61.7 (d), 62.3 (s), 73.2 (d), 79.2 (t), 85.4 (s), 119.1 (t), 128.2 (d), 135.6 (s), 135.8 (d), 173.3 (s). Exact mass calcd. for $C_{18}H_{26}O_4$ ($[M + Na]^+$) *m/z*: 329.1723; found: 329.1728.

Conclusions

In summary, a seven-step synthesis of **21** from 3,5-dimethylbenzoic acid has been developed. The chemistry extends the scope of a free-radical cyclization route to perhydroindans and reveals some interesting stereochemical features of the vinylogous Mukaiyama aldol condensation. Compound **21** is functionalized appropriately for the pursuit of the polyandranes at all positions except C_{11}. Modifications of this chemistry, incorporating more appropriate functionality at C_{11}, are being developed.

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