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Synthetic Studies Directed Toward Guianolides: An Organoiron Route to the 5,7,5 Tricyclic Ring System

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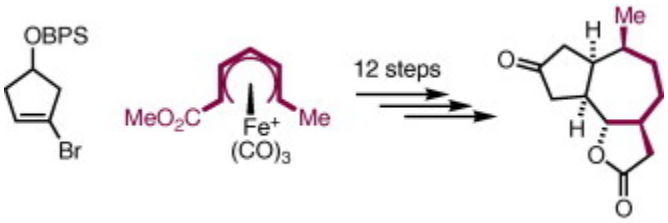
Abstract

A diastereoselective route to the 5,7,5-tricyclic core of the guianolides is presented. This route relies on Cope rearrangement of a divinylcyclopropane prepared by alkenyl Grignard addition to a (pentadienyl)iron(+1) cation, followed by oxidative decomplexation. An additional key reaction involves oxidative rearrangement of a 3,4-

epoxy-1,7-diol to generate a *γ*-lactone. The relative stereochemistry of this product was established by X-ray crystallography.

Graphical abstract



The guianolides are a family of sesquiterpenes characterized by a 5,7,5-fused tricyclic skeleton. The majority of these compounds possess a *trans*-γ-butryolactone ring, but differ with respect to the oxygenation and oxidation state(s) of carbons 2–5, 8, 10, and 11.[1] Representative members of this family include chinesiolide B (**1**, Fig. 1),[2] 10a-hydroxy-3-oxoguian-4-eno-12,6a-lactone (**2**),[3] cladantholide (**3**),[4] cynaropikrin (**4**),[5] and estafiatin (**5**).[6] While numerous syntheses of the pseudoguianolides have been reported,[7] there are considerably fewer total syntheses of the guianolides.8, 9

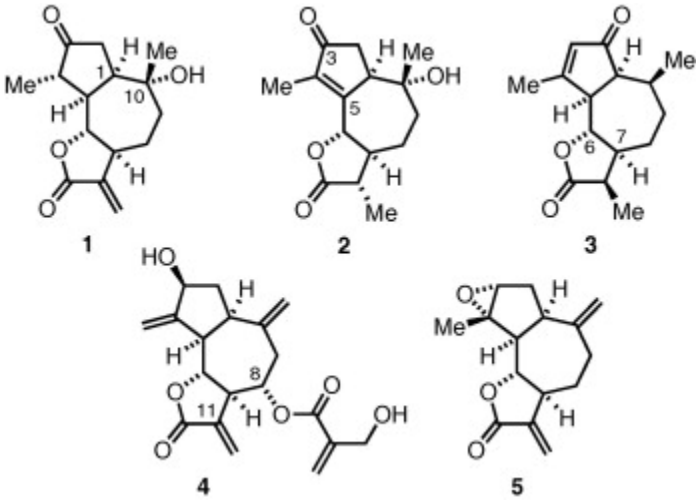
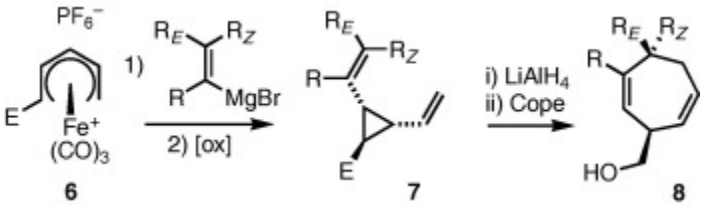


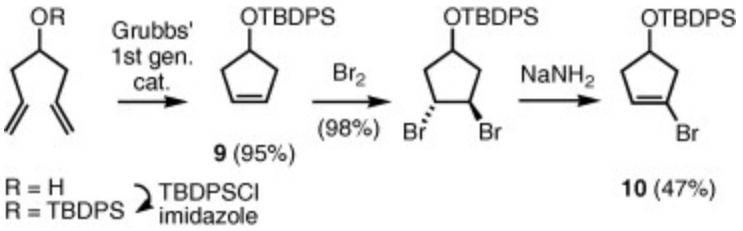
Figure 1. Representative guianolide natural products.

We have demonstrated that the exo-addition of alkenyl Grignard reagents to (1-methoxycarbonylpentadienyl)Fe(CO)3+ (**6**), followed by oxidative decomplexation affords divinylcyclopropanes (**7**, Scheme 1).[10] Ester reduction and Cope rearrangement of **7** generate cycloheptadienes (**8**). We herein report a route to the 5,7,5-fused tricyclic skeleton which utilizes this reactivity to generate the hydroazulene skeleton.



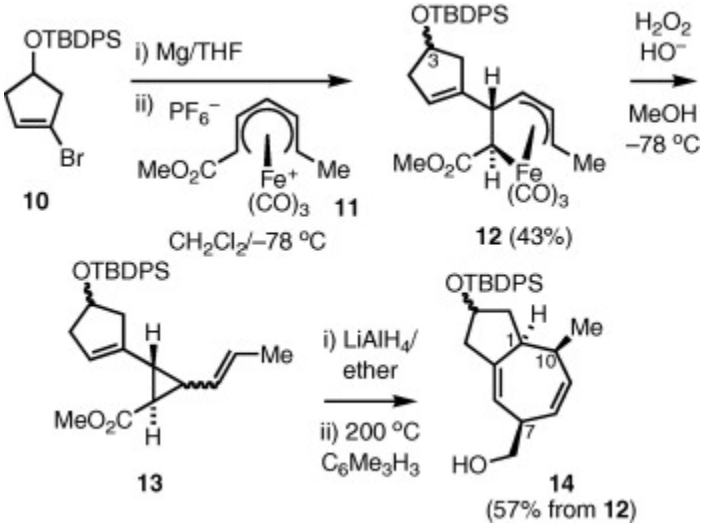
Scheme 1. (E = CO_2Me).

Protection of 1,6-heptadien-4-ol, followed by ring-closing metathesis afforded the cyclopentene **9** (Scheme 2). Addition of bromine gave the crystalline dibromide which upon *syn*-elimination with sodium amide gave the known[11] cyclopentenyl bromide **10**.



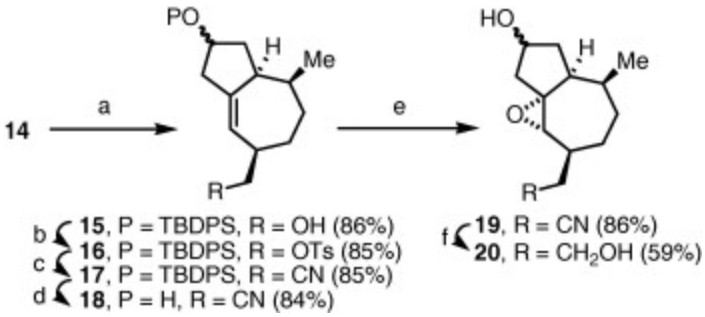
Scheme 2. (E = CO_2Me).

Generation of the Grignard reagent from **10** in THF, followed by addition to a solution of the known[12] (1-methoxycarbonylhexadienyl)Fe(CO)3+ cation (*rac*-**11**) in CH_2Cl_2 at −78 °C afforded the (pentenediyl)iron complex *rac*-**12** (Scheme 3). The presence of a doublet at δ 0.45 ppm in the ^{1}H NMR spectrum[13] of **12** is characteristic of a proton on a carbon σ-bound to iron. While the iron complex was formed as a ca. 1:1 mixture of diastereomers at the ether carbon (C3, guianolide numbering), this is inconsequential to the overall synthesis as this carbon will eventually become an sp^2 carbonyl carbon. Decomplexation of **12** with alkaline hydrogen peroxide gave an inseparable mixture of divinylcyclopropanes **13**, which were reduced with $LiAlH_4$ and subjected to thermal rearrangement to afford the hydroazulene **14**.[13] The relative stereochemistry at C1, C7, and C10 was tentatively assigned as indicated based on our previous results on the formation of **8** and other cycloheptadienes.[10]



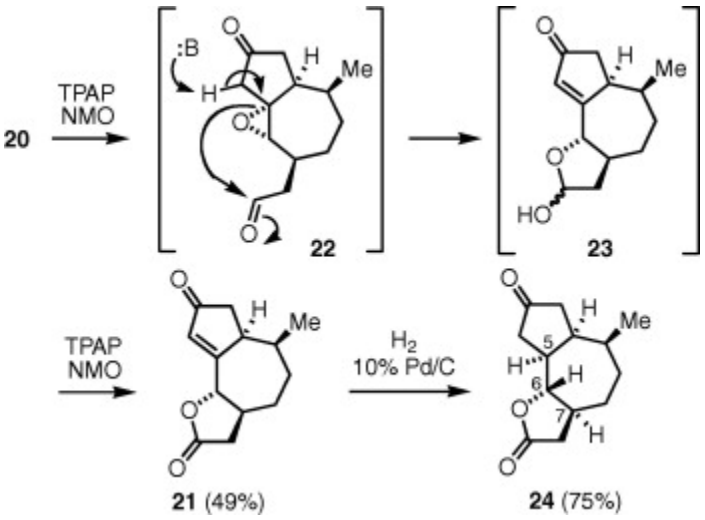
Scheme 3.

With the formation of the bicyclo[5.3.0]decane skeleton in place, our attention turned to appropriate functionalization of this scaffold. After considerable experimentation, the following pathway was successfully realized. Selective hydrogenation of the less substituted olefin with Wilkenson's catalyst gave the hexahydroazulene **15** (Scheme 4).[14] Extension of the C3 side chain was accomplished by tosylation followed by cyanide displacement to afford the nitrile **17**.[15] Cleavage of the silyl ether gave alcohol **18**, epoxidation of which occurs on the less hindered face to afford **19**.[16] Twofold reduction of **18** with DIBAL gave a diol **20**.



Scheme 4. Reagents and conditions: (a) H_2 (45 psi), 5% $RhCl(PPh_3)_3$, EtOH; (b) TsCl, DMAP, NEt_3, CH_2Cl_2; (c) NaCN, NaI, DMSO, 60 °C; (d) TBAF, THF; (e) mCPBA, $NaHCO_3$, CH_2Cl_2; (f) DIBAL, CH_2Cl_2, −78 °C to −40 °C (2×).

Oxidation of **20** with catalytic TPAP[17] in the presence of NMO (3.2 equiv) gave the lactone **21** (Scheme 5). This transformation presumably proceeds via oxidation of both the 1° and 2° alcohols to afford **22**, followed by β-elimination of the epoxide[18], and generation of the lactol **23**; oxidation of the lactol affords **21**. The relative configuration of **21** was unambiguously established by single crystal X-ray diffraction (Fig. 2)[19], which also corroborated the stereochemical assignments of hexahydroazulene **14** and epoxide **19**. Catalytic reduction of enone **21** gave a single ketone **24**. The relative configuration of **24** was assigned on the basis of its ^{1}H NMR spectral data;[20] in particular the signal for H-6 appears as a doublet of doublets (δ 4.07, J = 9.6, 9.6 Hz). The larger couplings are indicative of a trans-diaxial disposition of H-5, H-6, and H-7.



Scheme 5.

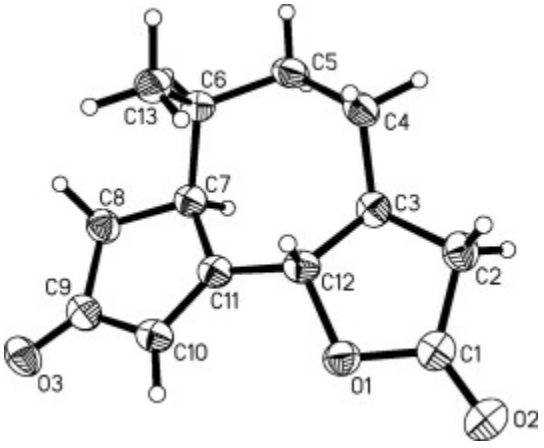


Figure 2. Molecular structure of 21**.**

In summary, the 5,7,5-tricyclic core of the guianolides has been prepared, including 5 contiguous stereocenters about the seven-membered ring. This route utilized nucleophilic attack on a (pentadienyl)iron(1+) cation followed by oxidative decomplexation for the generation of a divinylcyclopropane which upon Cope rearrangement gave the hydroazulene skeleton. Further elaboration included oxidation/ring opening of a β,γ-epoxy alcohol, subsequent lactol formation, and further oxidation to install the *trans*-γ-butyrolactone.

Acknowledgments

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13 *Selected spectral data:* **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.45 (d, J = 9.0 Hz, 1H), 1.02 and 1.03 (2 × s, 9H total), 1.84 (d, J = 6.0 Hz, 3H), 2.03–2.34 (m, 4H), 3.25–3.37 (m, 1H), 3.55–3.65 (m, 1H), 3.66 and 3.68 (2 × s, 3H total), 4.13–4.22 (m, 1H), 4.36–4.53 (m, 2H), 4.96–5.03 (m, 1H), 7.32–7.46 (m, 6H), 7.60–7.68 (m, 4H); FAB-HRMS *m/z* 607.1784 (calcd for $C_{32}H_{36}O_6SiFeLi$ ($M+Li^+$) *m/z* 607.1791). *Compound* **14:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J = 9.0 Hz, 3H), 1.08 and 1.09 (2 × s, 9H total), 1.52–1.74 (m, 2H), 1.87–1.99

(m, 1H), 2.22–2.3.11 (m, 1H), 2.32–2.49 (m, 2H), 2.86–2.96 and 3.10–3.20 and 3.28–3.43 (m, 2H total), 4.06–4.19 and 4.32–4.39 (2 × m, 1H total), 5.24–5.50 (m, 2H), 5.81–5.92 (m, 1H), 7.35–7.49 (m, 6H), 7.65–7.76 (m, 4H).

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15 *Compound* **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, J = 7.2 Hz) and 0.92 (d, J = 7.2 Hz) total 3H, 1.04 and 1.05 (2 × s, 9H total), 1.19–2.02 (m, 7H), 2.15–2.44 (m, 5H), 2.49–2.65 and 3.01–3.08 (m, 1H total), 3.96–4.06 and 4.27–4.35 (m, 1H total), 5.25 (d, J = 2.4 Hz) and 5.35 (d, J = 1.6 Hz) 1H total, 7.34–7.48 (m, 6H), 7.62–7.74 (m, 4H); FAB-HRMS *m/z* 450.2793 (calcd for $C_{29}H_{37}NOSiLi$ ($M+Li^+$) *m/z* 450.2804).

16 Repeated chromatography of the mixture of diastereomers lead to a small sample greatly enriched in one diastereomer. The relative configuration of this diastereomer was unassigned, and in general the mixture of diastereomers was used in the synthesis. *Compound* **19:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J = 7.2 Hz, 3H), 1.44 (dt, J = 13.5, 8.0 Hz, 1H), 1.49–1.90 (m, 8H), 2.01 (dd, J = 13.4, 9.8 Hz, 1H), 2.19 (br t, J = 8.0 Hz), 2.44–2.54 (m, 1H), 2.55–2.59 (m, 2H), 2.90 (d, J = 6.0 Hz, 1H), 4.39–4.48 (m, 1H); FAB-HRMS *m/z* 228.1586 (calcd for $C_{13}H_{19}NOSiLi$ ($M+Li^+$) *m/z* 228.1576).

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19 The crystallographic data for 21 has been deposited with the CCDC (CCDC 690098). This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retreiving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.ccdc.cam.ac.uk.

20 *Compound* **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 7.8 Hz, 3H), 1.39–1.54 (m, 2H), 1.56–1.70 (m, 1H), 1.90–2.11 (m, 3H), 2.18–2.43 (m, 5H), 2.44–2.59 (m, 2H), 2.65 (dd, J = 7.2, 16.2 Hz, 1H), 4.07 (dd, J = 9.6, 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 28.3, 30.1, 34.5, 37.5, 40.5, 40.7, 43.0, 44.1, 45.5, 86.6, 176.0, 217.7. FAB-HRMS *m/z* 223.1336 (calcd for $C_{13}H_{19}O_3$ ($M+H^+$) *m/z* 223.1334).