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# A synthetic pathway to diquinane and angular triquinane systems via an iron carbonyl promoted tandem [6+2] ene type reaction

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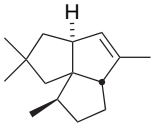
ABSTRACT

A model study is described on a new approach to the synthesis of diquinane and angular triquinane systems, via iron-promoted tandem [6+2] ene-type double cyclization followed by ozonolysis and intramolecular aldol reaction.

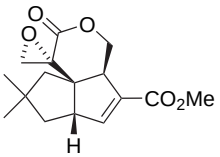


## 1. Introduction

Polyquinane natural products are a class of compounds that have molecular structures containing fused cyclopentane rings,[1] and have been of significant interest due to their biological activities since the first isolation in 1966.[2] Synthesis of triquinane natural products has continued to be an active area of research in organic chemistry since the first syntheses of hirsutene in the 1970s.[3] Pentalenene (**1**), an angular triquinane isolated from Streptomyces griseochrome,[4] is a key biogenetic precursor for the pentalenolactone family of antibiotics.[5] The structures of pentalenolactones possessing angular ring fusion led to considerable interest because of both biological, e.g., antitumor properties and synthetic challenge.[6] Several approaches have been developed since the first two syntheses by Matsumoto et al.[7] and by Paquette and Annis.[8] A squarate ester cascade using dissolving metal reduction,[9] [3+2] annulation strategy using carbene,[10] and keto acetal formation via Pauson/Khand bicyclization[11] are noteworthy pathways to generate the pentalenene structure. These have relatively fewer steps than earlier syntheses, but still require some intricate operations. Therefore, development of alternative approaches remains of significant interest.

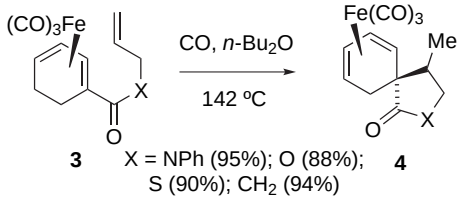


Pentalenene (**1**)



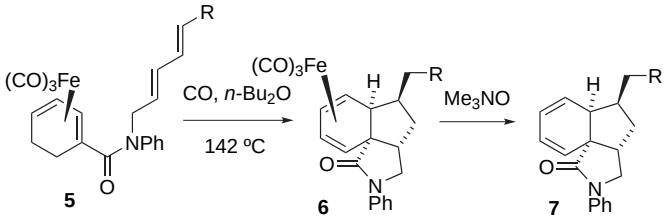
Pentalenolactone H (**2**)

In this paper we report a new method to construct an azatriquinane model system, modification of which is expected to be useful for making various angular triquinane natural products. This approach is based on a coupling reaction between a diene/$Fe(CO)_3$ complex and a pendent olefin that was developed in our laboratory several years ago, the outcome of which is equivalent to a [6+2] ene reaction (non-concerted).[12,13] A simple example of this transformation is shown in Eq. 1.



**3** X = NPh (95%); O (88%); S (90%); $CH_2$ (94%) **4** (1)

More recently we reported a stereospecific tandem double cyclization using cyclohexadiene/$Fe(CO)_3$ complexes and pendent conjugated dienes, exemplified here by the conversion of **5** to **6**, followed by demetalation to afford **7** as a single diastereomer (Scheme 1).[14]



**Scheme 1.**

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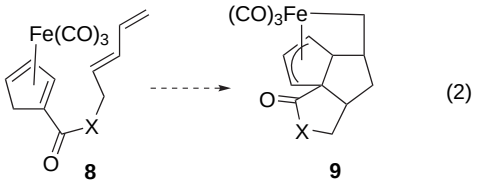
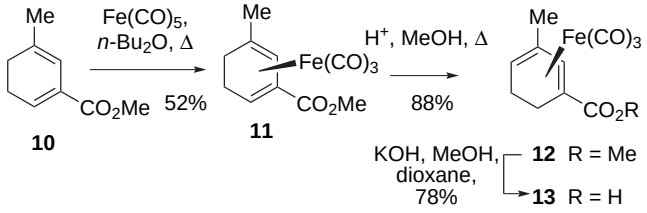
Application of this method to the construction of angular triquinane structures would ideally replace the cyclohexadiene substrate with an analogous cyclopentadiene, but there are two major obstacles to this direct approach: (1) Cyclopentadiene/$Fe(CO)_3$ complexes, such as **8** (Eq. 2) are not accessible (reactions of iron carbonyls with cyclopentadiene result in the formation of cylopentadienyl complexes[15]). (2) A tandem double cyclization such as that shown in Eq. 1 using such cyclopentadiene systems would result in the formation of a π-allyl/iron complex **9** (Eq. 2), that would require a difficult demetallative functionalization to afford a useful organic compound. Therefore, a cyclohexadiene that can be subjected to ring contraction is preferred, and for this study we chose to employ a methyl-substituted diene that could be converted to a cyclopentenone via ozonolysis and aldol cyclization.



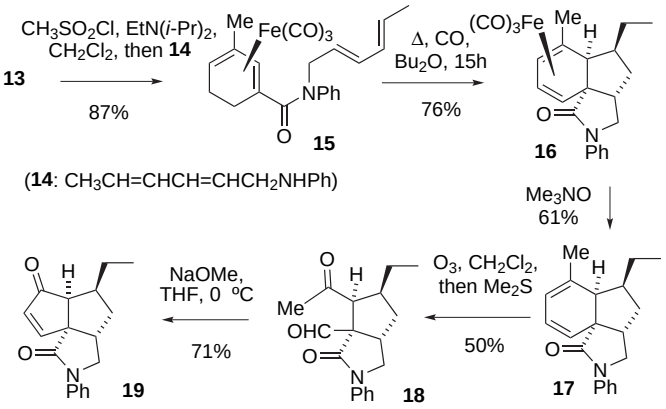

The key precursor for this endeavor, iron-complexed acid **13** was prepared as shown in Scheme 2.[13,16] Known[17] diene ester **10** was converted to (racemic) complex **11** by reaction with pentacarbonyliron. For the subsequent tandem ene-type cyclization, the carboxyl group is preferred at the diene terminus, so complex **11** was subjected to acid-catalyzed rearrangement to **12**,[18] which was hydrolyzed to afford acid **13**. Complex **12** is a known compound, but was prepared by a different route to that shown in Scheme 2.[16]




**Scheme 2.**

Diene **14**, prepared by reductive amination from 2,4-hexadienal (sorbaldehyde) and aniline,[19] was reacted with the methanesulfonyl mixed anhydride from complex **13** to afford amide **15** (Scheme 3). To effect double cyclization of **15**, standard thermal conditions[14] (reflux, di-*n*-butyl ether) were found to give good yield of **16**. The structure and stereochemistry of **16** was assigned by analogy with our earlier work that established the structures of related compounds **6** (Scheme 1).[14] Removal of the iron carbonyl moiety from the cyclized product **16** to afford diene **17** was effected by treatment with $Me_3NO$/benzene[20] or in similar yield by oxidation using $CuCl_2$/EtOH.[21] Ozonolysis of **17** gave satisfactory conversion to keto aldehyde **18**; this direct method was higher yielding than $OsO_4$ promoted tetrahydroxylation followed by periodate cleavage. Azatriquinane **19** was secured from **18** by intramolecular aldol reaction and in situ dehydration using NaOMe in THF. The structure of **19** is consistent with the $^1H$ NMR spectrum, which shows the presence of the enone protons at δ 6.25 and 6.73 ppm.

In summary, a novel method for the construction of the angular triquinane skeleton is reported using a combination of iron-promoted tandem double ene-type cyclization followed by ring contraction. Modifications of the pendent diene subunit should allow incorporation of functional groups on the fused ring structure.[22]




**Scheme 3.**

The model study reported here used an amide substrate since these systems are well behaved in the tandem double cyclization. Future work will focus on the application of this methodology to all-carbon systems in anticipation of producing fused five-membered carbocyclic structures that are more appropriate for consideration of synthetic approaches to compounds related to pentalenene.

## 2. Experimental section

### 2.1. General methods

All reactions were carried out under inert atmosphere of dry, deoxygenated argon, unless otherwise stated. All glassware used were oven dried overnight at 140 °C or flame dried immediately prior to use. Organic solvents were purified by distillation under Ar prior to use as follows: THF, diethyl ether, and benzene from Na/benzophenone; $CH_2Cl_2$ from $CaH_2$; *n*-$Bu_2O$ from Na. All other solvents were used as purchased. Column chromatography was performed on flash grade silica gel (0.04–0.063 mm). Eluting solvents are reported as v/v percent mixtures. Preparative thin layer chromatography was performed on E. Merck silica gel $F_{254}$ 0.5 or 2.0 mm thickness plates. CO was used as purchased (Matheson Tri-Gas, C.P. grade). $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian Inova AS400 (400 MHz for $^1H$) spectrometer using the solvent noted, and referenced to the solvent or TMS as internal standard. Mass spectra were recorded in-house on a Kratos MS25A instrument. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected.

*2.1.1. Tricarbonyl(methyl 5-methylcyclohexa-1,5-dienecarboxylate) iron (**11**).* Ester **10** (288 mg, 1.89 mmol) was dissolved in 3.5 mL of *n*-$Bu_2O$, and 0.41 mL of pentacarbonyliron (594 mg, 3.03 mmol, 1.6 equiv) was added. The reaction mixture was refluxed under Ar for 43 h, cooled to rt, then filtered through Celite, and the filter pad was rinsed with *n*-$Bu_2O$ [*caution*: pyrophoric iron may be produced by thermal decomposition of pentacarbonyliron; do not allow the residue to become dry in air]. Removal of solvent by rotary evaporation, followed by flash chromatography purification (hex/EA 10:1) afforded complex **11** (277 mg, 52% yield) as a yellow oil. $R_f$=0.5 (hex/EA 15:1); $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.53–1.60 (m, 1H), 1.66 (s, 3H), 1.67–1.72 (m, 1H), 1.83–1.95 (2H), 3.64 (t, 1H, *J*=8.0 Hz), 3.81 (s, 3H), 6.00 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 12.5, 22.9, 25.5, 33.4, 39.8, 43.5, 55.1, 120.2, 133.6, 208.7; HRMS-FAB calcd for $[C_{12}H_{13}O_5Fe]^+$ ($MH^+$) *m*/*z* 293.0112, found 293.0136.

*2.1.2. Tricarbonyl(methyl 3-methylcyclohexa-1,3-dienecarboxylate) iron (**12**).* Ester **11** (190 mg, 0.65 mmol) was dissolved in a mixture

of 1.5 mL of MeOH and 0.15 mL of concd $H_2SO_4$ (previously degassed with Ar for 1 min) and refluxed under Ar for 24 h. The reaction mixture was cooled and added to an excess of ice/water, then extracted with ether (10 mL×3). The combined extracts were washed with water, then aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation of solvent, followed by flash column chromatography of the residue afforded rearranged ester **12** as a pale yellow oil (167 mg, 88%). $R_f$=0.49 (hex/EA 15:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.35–1.42 (m, 1H), 1.65–1.78 (m, 1H), 1.89–1.98 (m, 1H), 2.07–2.18 (m, 1H), 2.09 (s, 3H), 3.35 (t, 1H, $J$=8.0 Hz), 3.71 (s, 3H), 5.93 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.5, 29.2, 35.5, 46.6, 49.9, 123.2, 128.9, 209.9. NMR data for this product are consistent with that reported by Bandara et al.[16]

*2.1.3. Tricarbonyl(3-methylcyclohexa-1,3-dienecarboxylic acid)iron (**13**).* To a solution of complex **12** (130 mg, 0.45 mmol) in a mixture of dioxane (0.7 mL) and methanol (0.7 mL), which was purged with Ar for 10 min, was added 30% aqueous KOH solution (0.36 mL), which was also bubbled with Ar for 10 min before addition. After the reaction solution was stirred under Ar at rt for 24 h, 2 N HCl was added to adjust to pH=2–3. The aqueous solution was extracted with $CH_2Cl_2$ (3 mL×3). The combined organic layer was filtered through Celite, washed with brine (2 mL×2), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Flash chromatography (hex/EA 2:1) afforded acid **13** (97 mg, 78%). $R_f$=0.19 (hex/EA 2:1); mp 182–185 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.28–1.35 (m, 1H), 1.60–1.70 (m, 1H), 1.80–1.90 (m, 1H), 1.90–2.00 (m, 1H), 2.07 (s, 3H), 3.40 (br, 1H), 5.96 (s, 1H), 12.30–12.15 (br, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.0, 23.3, 26.0, 63.9, 67.4, 89.1, 103.5, 174.0, 211.6; HRMS-FAB calcd for $[C_{11}H_{11}O_5Fe]^+$ ($MH^+$) $m/z$ 278.9956, found 278.9952.

*2.1.4. Tricarbonyl[1-4-η-3-methylcyclohexa-1,3-dienecarboxylic acid (N-phenyl)hexa-2,4-dienyl amide]iron (**15**).* Acid **13** (69 mg, 0.248 mmol) and 80 mg of 4 Å molecular sieves in 2 mL of $CH_2Cl_2$ under Ar at 0 °C were treated with 82 μL of DIPEA (0.496 mmol, 2 equiv), followed by dropwise addition of 0.12 mL of $CH_3SO_2Cl$ (0.323 mmol, 1.3 equiv) over 5 min, and the solution was stirred at 0 °C for 1 h. The flask was rotary evaporated and 2 mL of $CH_2Cl_2$ containing 110 μL of *N*-phenyl-2,4-hexadienylamine (0.496 mmol, 2 equiv) and 110 μL of DIPEA was added. The mixture was stirred at rt for 24 h, followed by removal of solvent and purification by flash chromatography, to afford 87 mg (81% yield) of **15** as a light brown oil, along with 5 mg of recovered **14**. Based on reacted starting material, the yield was 87%. $R_f$=0.34 (hex/EA 9:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.26–1.29 (2H), 1.56–1.65 (m, 2H) 1.70 (d, $J$=8.0 Hz, 3H), 1.73–1.84 (m, 2H), 1.89 (s, 3H), 3.25 (1H), 4.13 (dd, 1H, $J$=14.0, 6.6 Hz), 4.45 (dd, 1H, $J$=14.0, 6.4 Hz), 5.44 (s, 1H), 5.53–5.63 (m, 1H), 5.91–6.01 (m, 1H), 7.18 (dd, 2H, $J$=8.4, 1.2 Hz), 7.32 (m, 1H), 7.40–7.43 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 18.3, 22.0, 25.0, 26.7, 54.2, 66.2, 68.2, 87.1, 101.5, 125.6, 127.6, 128.0, 129.6, 129.8, 131.1, 133.9, 143.8, 173.0; HRMS-FAB calcd for $[C_{23}H_{24}NO_4Fe]^+$ ($MH^+$) $m/z$ 434.1055, found 434.1044.

*2.1.5. Tricarbonyl(6-9-η-6-methyl-5-ethyl-2-phenyl-2,3,3a,4,5,5a-hexahydro-2-azacyclo penta[c]inden-1-one)iron (**16**).* Complex **15** (36 mg, 0.083 mmol) was refluxed in 15 mL of freshly distilled *n*-$Bu_2O$ for 15 h under CO (balloon). The mixture was cooled to rt and filtered through Celite. Removal of solvent by rotary evaporation, followed by chromatographic separation (preparative TLC) of the residue afforded 22.3 mg (62%) of **16** as a pale yellow viscous oil along with 6.5 mg of recovered starting material and a trace amount of demetalated product **17**. (Yield based on reacted starting material=76%). $R_f$=0.63 (hex/EA 4:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.87–0.94 (m, 2H), 0.97 (t, 3H $J$=7.2 Hz), 1.37–1.51 (m, 1H), 1.62 (s, 3H), 1.89–1.99 (m, 2H), 2.38 (d, 1H, $J$=8.0 Hz), 2.69 (dd, 1H, $J$=9.4, 1.0 Hz), 2.95 (dd, 1H, $J$=6.4, 1.6 Hz), 3.44 (dd, 1H, $J$=6.4, 1.6 Hz), 4.06 (dd, 1H, $J$=9.6, 7.2 Hz), 5.15 (d, 1H, $J$=4.2 Hz), 5.34 (dd, 1H, $J$=6.8, 4.2 Hz), 7.13–7.64 (5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 16.3, 17.8, 19.1, 25.6, 31.2, 52.3, 60.4, 62.2, 73.7, 115.4, 120.0, 126.4, 129.5 139.3, 155.9, 158.4 160.6, 165.0; HRMS-FAB calcd for $[C_{23}H_{24}NO_4Fe]^+$ ($MH^+$) $m/z$ 434.1055, found 434.1061.

*2.1.6. 6-Methyl-5-ethyl-2-phenyl-2,3,3a,4,5,5a-hexahydro-2-azacyclopenta[c]inden-1-one (**17**).* Complex **16** (12 mg, 0.027 mmol) was added to a mixture of $Me_3NO$ (40 mg, 0.55 mmol) and 2 mL of dried benzene. The reaction mixture was heated at 40–50 °C for 3 h, then cooled to rt. Filtration through Celite, followed by rotary evaporation of solvent and PLC purification afforded 4.9 mg (61%) of **17** as a colorless viscous oil. $R_f$=0.18 (hex/EA 9:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.85–0.88 (t, 3H, $J$=7.2 Hz), 0.92–1.02 (m, 2H), 1.23–1.30 (m, 1H), 1.33–1.41 (m, 1H), 1.82 (s, 3H), 2.0 (dd, 1H, $J$=6.0, 4.0 Hz), 2.35–2.39 (m, 1H), 2.61–2.70 (m, 1H), 2.97 (d, 1H, $J$=6.8 Hz), 3.60 (d, 1H, $J$=6.8 Hz), 4.11 (dd, 1H, $J$=10.0, 7.4 Hz), 5.40 (d, 1H, $J$=6.5 Hz), 5.77 (dm, 1H, $J$=9.4 Hz), 5.92 (dd, 1H, $J$=9.4, 6.5 Hz), 7.13–7.75 (5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 12.3, 21.2, 25.1, 26.5, 39.1, 41.3, 42.2, 51.6, 52.3, 119.5, 121.6, 123.5, 124.4, 129.0, 133.9, 141.7, 153.3, 174.0; HRMS-FAB calcd for $[C_{20}H_{24}NO]^+$ ($MH^+$) $m/z$ 294.1858, found 294.1851.

*2.1.7. 4-Acetyl-5-ethyl-octahydro-3-oxo-2-phenylcyclopenta[c]-pyrrole-3a-carbaldehyde (**18**).* Ozone was passed through a dichloromethane (1.2 mL) solution of compound **17** (6.9 mg, 0.024 mmol) at −78 °C, terminating immediately upon observation of the distinctive blue color of ozone. Neat dimethyl sulfide (0.3 mL) was then added dropwise to the cold solution (−78 °C). The resultant mixture was warmed to rt and stirred for 3 h, and then the solvent was removed under reduced pressure. Preparative TLC purification of the crude product gave 3.5 mg (50%) of **18** as a colorless oil. $R_f$=0.35 (hex/EA 5:1); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.94 (t, 3H, $J$=7.2 Hz), 1.29–1.37 (m, 1H), 1.40–1.47 (m, 1H), 1.74–1.77 (m, 1H), 2.02 (s, 3H), 2.30–2.39 (m, 1H) 2.82 (d, 1H, $J$=3.8 Hz), 3.24 (d, 1H, $J$=8.0 Hz), 3.80 (dd, 1H, $J$=8.0, 3.8 Hz), 7.02–7.68 (5H), 9.98 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 11.9, 16.7, 25.2, 28.6, 34.6, 39.8, 46.1, 51.3, 67.1, 121.5, 124.0, 128.1, 170.2, 200.3, 203.6; HRMS-EI calcd for $[C_{18}H_{21}NO_3]^+$ ($M^+$) $m/z$ 299.1521, found 299.1528.

*2.1.8. 5-Ethyl-2,3,3a,4,5,5a-hexahydro-2-phenylpentaleno[1-c]pyrrole-1,6-dione (**19**).* A solution of aldehyde **18** (3.5 mg, 0.0117 mmol) in 1 mL of THF was prepared at 0 °C. The solution was stirred for 5 min, and then NaOMe was added. The resulting solution was stirred for 2 h, then warmed to rt and stirred for 4 h. The mixture was added to water, and the product extracted with ether (5 mL×3). The combined extracts were dried ($MgSO_4$), evaporated, and purified by preparative TLC. The title compound **19** was obtained as a pale yellow viscous oil (71% yield). $R_f$=0.15 (hex/EA 9:1); $^1$H NMR ($C_6D_6$, 400 MHz) $\delta$ 0.93 (t, 3H, $J$=7.4 Hz), 1.26 (m, 2H), 1.32 (m, 1H), 1.49–1.53 (m, 1H), 1.75–1.78 (m, 1H), 2.21–2.28 (m, 1H), 2.36–2.43 (m, 1H), 3.48 (d, 1H, $J$=8.1 Hz), 3.92 (dd, 1H, $J$=8.1, 3.8 Hz), 6.25 (d, 1H, $J$=9.1 Hz), 6.73 (d, 1H, $J$=9.1 Hz), 7.15–7.54 (5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 12.5, 22.9, 25.5, 33.4, 39.8, 43.5, 49.9, 55.1, 120.2, 123.2, 128.9, 133.6, 142.8, 150.2, 207.7; HRMS-EI calcd for $[C_{18}H_{19}NO_2]^+$ ($M^+$) $m/z$ 281.1416, found 281.1409.

## Acknowledgements

We are grateful to Case Western Reserve University and the National Science Foundation (CHE-0743234) for financial support of this research.

## Supplementary data

Copies of $^{1}H$ and $^{13}C$ NMR spectra of compounds **11**–**19** can be found. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.018. This data include MOL files and InChiKey of the most important compounds described in this article.

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