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Synthetic study on the angular triquinanes

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Abstract: The synthesis of an angular triquinane, which could serve as a suitable platform for the synthesis of several natural products (panaginsene, silphinene, senoxydene) is described. The synthesis is based on two consecutive cyclopentene annulations, where alkenes were used as latent carbonyl functionalities (*via* Wacker reaction), and cyclopentenone annulation was effected by aldol condensation.

Keywords: cyclopentane; natural products; organic synthesis; Wacker oxidation; aldol condensation.

INTRODUCTION

Among the thousands of structurally diverse, naturally occurring sesquiterpene compounds, the subgroup of triquinanes, although not numerous, occupies a prominent place, due to peculiar structures and a range of biological activities. These polycyclic compounds are assembled from condensed cyclopentane rings and, depending on the fusion pattern, can be classified as linear, angular, or propellane (Figure 1). Triquinane structural subunits are also embedded into tetraquinane skeletons. Not surprisingly, they have attracted considerable interest from the synthetic community.[1]

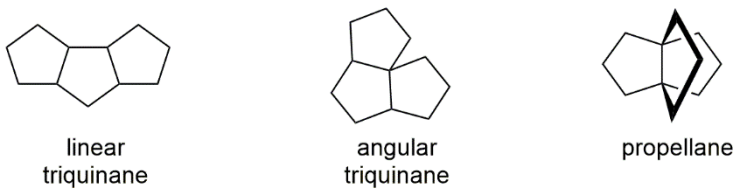

Figure 1: Three types of triquinane fusion

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Naturally occurring angular triquinanes comprise four skeletal types, namely isocomanes, silphinanes, pentalenanes and silphiperfolanes (Figure 2). Some of them exhibit interesting biological activities, such as subergorgic acid (**1**, member of the isocomane family), which is cardiotoxic,[2] but also shows antiholinesterase activity,[3] and hence the ability to act as antidote against Soman in mice.[4] Oxygenated congeners of pentalenene **2**, such as pentalenolactone, show antibiotic activity.[5] Silphinene **3** is a biosynthetic precursor of oxygenated products such as aspergilanes,[6] or penifulvins; penifulvin A possesses significant insecticidal activity.[7]

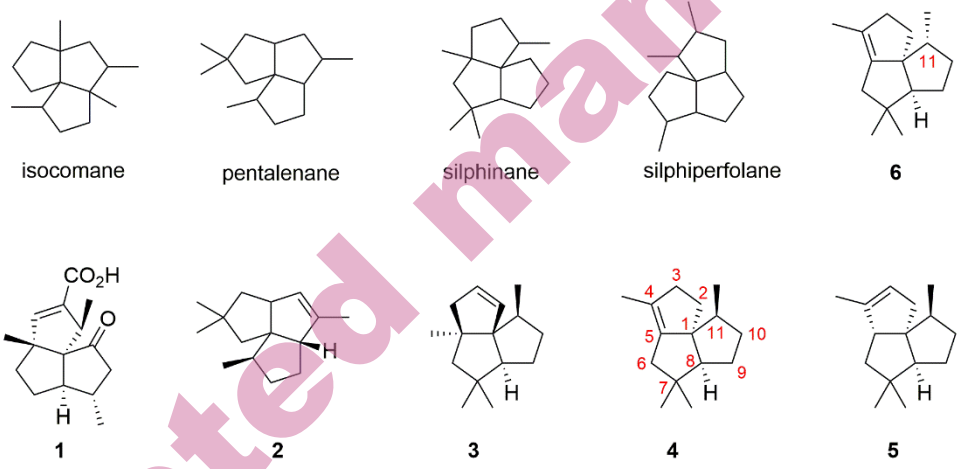


Figure 2: Examples of naturally occurring angular triquinanes

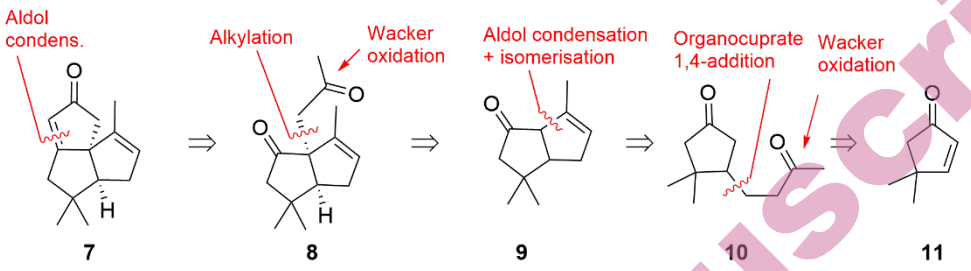
We became interested in silphinene **3** and its congeners – panaginsene **4**[8] and senoxydene **5**. These compounds share the common angular triquinane skeleton, with some differences in the position of the alkene bond and one methyl substituent. One stereochemical difference is also of note: the methyl group at C-11 may be of either *trans*-configuration (in panaginsene and senoxydene), or *cis*-oriented (in silphinene), with respect to the cyclopentene ring. Interestingly, panaginsene was initially assigned as *cis*-configured isomer **6**, which was later revised (corrected structure: **4**).[9] Nine total syntheses of silphinene have been reported, the first one by Ito and coworkers, who used bicyclopentadiene as the starting material.[10] Paquette and Leone-Bay constructed the triquinane skeleton by iterative application of 3-oxo-organocuprate 1,4-addition/aldol condensation reaction tandem.[11] Sternbach and coworkers relied on intramolecular Diels-Alder reaction, followed by oxidative fragmentation of the transient tricycle to the diquinane intermediate.[12] The synthesis by Wender and Ternansky hinges on arene-olefin meta-photocycloaddition, followed by reductive cleavage of cyclopropane ring in the tetracyclic intermediate.[13] Crimmins and Mascarella used

a tactical combination of reactions: [2+2] alkene photocycloaddition/cyclobutane fragmentation to access racemic **3**.[14] Synthetic approach by Nagarajan and Rao is based on two cyclopentane annulations, the first by intramolecular Horner-Wadsworth- Emmons reaction and the second by a radical 5-*exo*-cyclization.[15] Yamamura and coworkers created a tricyclic intermediate by an intramolecular cycloaddition of electrochemically generated phenoxy cation; this intermediate was then elaborated into a triquinane framework.[16] Franck-Neumannm, Miesch and Gross developed "the cyclobutenic way" to silphinene, which comprises cyclopropanation of bicyclo[3.2.0.]hept-6-ene cycloadduct, followed by solvolysis of a highly strained tricyclic intermediate.[17] Fraser-Reid and Dickson used the chiron approach and synthesized (–)-**3** from mannose.[18] Two syntheses of panaginsene have been reported: Lee and Geum used as a key step an intramolecular cycloaddition *via* biradical intermediate,[9] whereas Chakraborty and Singh relied on McMurry coupling for the cyclopentene ring closure.[19] As for senoxydene, two syntheses have been reported: Paquette and coworkers used intramolecular ene-cyclization for the stereoselective formation of the key bicyclic intermediate,[20] whereas Ito and coworkers exploited the common intermediate from their previous synthesis of silphinene.[21]

RESULTS AND DISCUSSION

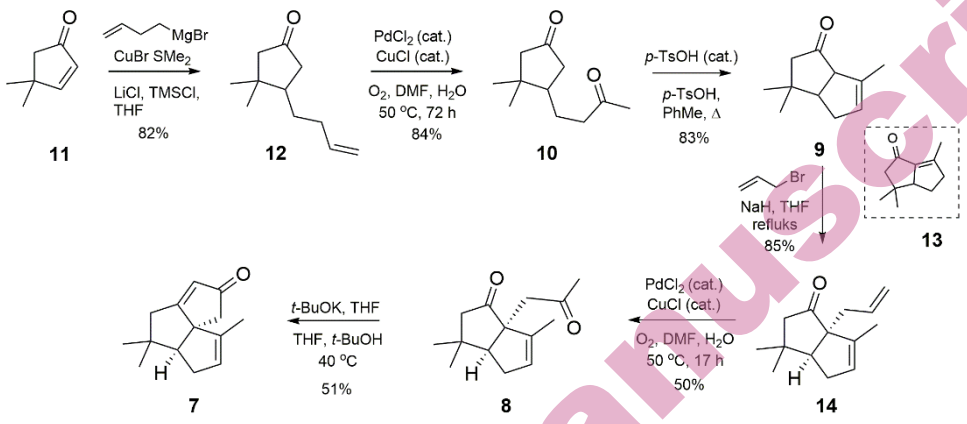
We set out to develop a method that would allow for efficient construction of the angular triquinane **7**, which contains the skeleton of these three congeners, and where the configuration of the C-11 methyl group could be established subsequently (*i.e.*, in late stages of synthesis), possibly giving rise to both diastereoisomers.

Our retrosynthetic analysis is blueprinted in Scheme 1. Cyclopentenone disconnection in **7** by aldol condensation transform simplifies the target to bicyclic ketone **8**, which could be obtained from **9** by tactical combination of reactions: allylation/Wacker oxidation. Bicyclic ketone **9** should be accessible by aldolization/isomerization tandem reaction; we were aware that this step would need a study on the reaction conditions/product distribution relationship. The dicarbonyl precursor **10** of enone **9** could be prepared by Wacker oxidation of 3-butenylcyclopentanone derivative (not shown), on its turn obtainable from known 4,4-dimethyl-2-cyclopentene-1-one (**11**).[22]



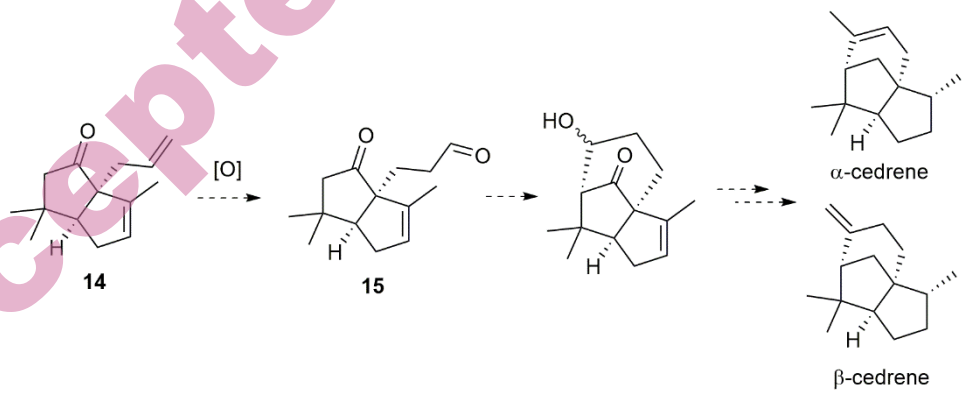
Scheme 1: Retrosynthetic analysis of angular triquinane 7

The synthesis commenced with 1,4-addition of a butenyl cuprate reagent to the known 4,4-dimethylcyclopent-2-ene-1-one (**11**), which afforded the adduct **12** (Scheme 2). This transformation was reported earlier;[20b] however, modifying the reaction conditions – activation by trimethylsilyl-chloride and lithium chloride – improved the yield considerably (82%, vs. 65% in the previous publication).[23] Wacker oxidation of **12** under an oxygen atmosphere required 72 h at 50 °C, but provided dione **10** in 84% yield. Various reaction conditions were tried to accomplish the cyclization step (*i.e.*, **10** → **9**), including potassium hydroxide in aqueous ether, potassium *tert*-butoxide in *tert*-butanol, or in THF, pyrrolidine (alone, or in the presence of acetic acid, or *p*-TsOH), but in all cases mixtures of conjugated (**13**) and deconjugated (**9**) product were obtained. Finally, we found that the cyclization could be performed in boiling toluene, in presence of catalytic amounts of *p*-TsOH, to provide the desired bicyclic enone **9** in 83% yield (accompanied with 9% of the conjugated isomer **13**). The next step was the installation of acetonyl moiety, to obtain dione **8**. From several synthons available as synthetic equivalents of "acetonyl cation" we chose the structurally simplest one – allyl bromide – for two reasons: a) minimization of steric hindrance, and b) the allylation product **14** should be amenable also to aldehyde **15** – an intermediate whose role is explained below (in Scheme 3). Regioselective allylation of **9** was promoted by sodium hydride in boiling THF, where single regio- and diastereoisomer **14** was obtained (85%). It is of note that the regioselectivity in reactions of this type is highly dependent on substrate structure; thus, in the allylation of the structurally related bicyclic system, the less substituted α-position of the ketone required protection, in order to secure allylation at the more substituted α'-position.[20] Wacker oxidation of **14** proceeded much faster than the previous one (*i.e.*, **12** → **10**), and provided bicyclic dione **8** in 50% yield (accompanied with 10% of aldehyde **15**). Upon treatment with potassium *tert*-butoxide in *tert*-butanol, **8** cyclized into triquinane **7** (51%), thus providing the target molecule in six steps (12% overall yield) from the starting 4,4-dimethylcyclopent-2-ene-1-one (**11**).



Scheme 2: Synthesis of triquinane 7

The scope of sesquiterpene natural products targeted by this methodology is not limited to angular triquinanes, but extends to bridged diquinane, *i.e.*, cedrenes. Thus, regioisomeric oxidation of intermediate **14** should provide aldehyde **15**, from which the assembly of cedrene skeleton would be accomplished by an intramolecular aldol reaction (Scheme 3). In this way, a single synthetic intermediate (*i.e.*, **14**) would provide access to several members of two distinct classes of quinane natural products.



Scheme 3: Towards α- and β-cedrene

CONCLUSION

To summarize, an efficient synthesis of the advanced intermediate **7** for the synthesis of triquinane sesquiterpenes (panaginsene, senoxydene and silphinene) is described, which relies on iterative application of the Wacker oxidation/aldol condensation tactical combination of reactions (*i.e.*, **12** → **9**; **14** → **7**). Research aiming to the conversion of this intermediate into the target natural products, as

well as extension of this methodology to the synthesis of cedrenes (according to Scheme 3), is underway in our laboratories.

EXPERIMENTAL

General experimental details

All chromatographic separations were performed on Silica gel 60 (0.063-0.2 mm), Merck. Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on Varian/Agilent 400 (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz in deuterated chloroform, if not otherwise stated. Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (*J*) are in Hz. IR spectra were recorded on Thermo Scientific Nicolet Summit FT-IR instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Orbitrap Exploris 240 spectrometer.

The physical data and NMR spectra of the synthesized compounds are given in Supplementary material to this paper.

*4-(But-3-en-1-yl)-3,3-dimethylcyclopentan-1-one (**12**)*

To a soluton of CuBr·SMe$_2$ (9.7 g, 47 mmol, 2.16 eq) and LiCl (2 g, 47 mmol, 2.16 eq) in THF (50 mL) a solution of Grignard reagent prepared from magnesium turnings (1.42 g, 58.44 mmol) and 4-bromo-1-butene (6 g, 44.44 mmol) was added dropwise at –78 °C, and the reaction mixture was stirred for additional 30 min. A solution of ketone **11** (2.4 g, 21.8 mmol, 1 eq) and TMSCl (7 mL, 5.98 g, 55 mmol, 2.52 eq) in THF (51 mL) was added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature overnight, quenched with acetic acid (22 mL) and stirred for 1.5 h. The mixture was transfered into a beaker and saturated soluton of NaHCO$_3$ (160 mL) was added in portions. The mixture was filtered trough Celite and extracted three times with methylene chloride. The combined organic layer was washed with brine, and dried over anh. MgSO$_4$, filtered, concentrated at rotovap and purified by dry-flash chromatography (petroleum ether/ethyl acetate = 7/1) to afford 2.96 g (82%) of product **12** as a pale yellow oil.

*3,3-Dimethyl-4-(3-oxobutyl)cyclopentan-1-one (**10**)*

Ketone **12** (610 mg, 3.67 mmol, 1 eq) was added to a solution of PdCl$_2$ (40 mg, 0.225 mmol, 0.06 eq) and CuCl (150 mg, 1.51 mmol, 0.41 eq) in DMF (2.8 mL) and H$_2$O (0.5 mL, 27.76 mmol, 7.56 eq) under an O$_2$ atmosphere. The reaction mixture was stirred at 50 °C for 72 h, then diluted with water and extracted with Et$_2$O. Organic layer was washed with water and brine, dried over anh. MgSO$_4$, filtered, concentrated at rotovap and purified by dry-flash chromatography (petroleum ether/ethyl acetate = 7/1) to afford 561 mg (84%) of product **10** as pale yellow oil.

*3,3,6-Trimethyl-3,3a,4,6a-tetrahydropentalen-1(2H)-one (**9**)*

TsOH·2H$_2$O (55 mg, 0.29 mmol, 0.22 eq) was added to a solution of diketone **10** (240 mg, 1.32 mmol) in toluene (20 mL). The flask was equiped with Deak-Stark apparatus and the reaction mixture was refluxed for 5 h. The mixture was transfered into a separatory funnel, diluted with DCM, washed with saturated solution of NaHCO$_3$, dried over anh. MgSO$_4$, concentrated at rotovap and purified by dry-flash chromatography (petroleum ether/ethyl acetate = 95/5) to afford 182 mg (83%) of product **9** (R_f = 0.32 (petroleum ether/ethyl acetate = 95/5)) followed by 15 mg (9%) of conjugated ketone **13** (R_f = 0.17 (petroleum ether/ethyl acetate = 95/5)).

*6a-Allyl-3,3,6-trimethyl-3,3a,4,6a-tetrahydropentalen-1(2H)-one (**14**)*

A solution of ketone **9** (200 mg, 1.22 mmol, 1 eq) in THF (3 mL) was added to a suspension of NaH (73 mg (60%), 1.83 mmol, 1.5 eq) in THF (1 mL), mixture was heated to reflux and stirred for 30 min when allyl-bromide (0.21 mL, 2.43 mmol, 2 eq) was added. After 4 h, more allyl-bromide was added (0.21 mL, 2.43 mmol, 2 eq) and refluxing was contiued overnight. Reaction was quenched with water, acidified with few drops of 1.5 M HCl, extracted with DCM, washed with brine, dried over anh. $MgSO_4$, filtered, concentrated at rotovap and purified by dry-flash chromatography (petroleum ether/ethyl acetate = 95/5) to afford 213 mg (85%) of product **14** as colorless oil.

*3,3,6-Trimethyl-6a-(2-oxopropyl)-3,3a,4,6a-tetrahydropentalen-1(2H)-one (**8**)*

Ketone **14** (64 mg, 0.31 mmol, 1 eq) was added to a solution of $PdCl_2$ (16.6 mg, 0.09 mmol, 0.3 eq) and CuCl (40.3 mg, 0.41 mmol, 1.3 eq) in DMF (0.7 mL) and H_2O (0.128 mL) under an O_2 atmosphere. The reaction mixture was stirred at 50 °C for 17 h, then diluted with water and extracted with Et_2O. Organic extract was washed with water and brine, dried over anh. $MgSO_4$, filtered, concentrated at rotovap and purified by column chromatography (hexane/ethyl-acetate = 9/1) to afford 35 mg (51%) of product **8** as colorless oil.

*5,5,8-Trimethyl-4,5,5a,6-tetrahydrocyclopenta[c]pentalen-2(1H)-one (**7**)*

A solution of diketone **8** (18 mg, 0.082 mmol, 1 eq), t-BuOK (20 mg, 0.175 mmol, 2.14 eq) and t-BuOH (0.1 mL) in THF (3.5 mL) was heated to 40 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with water and few drops of 1.5 M HCl, extracted with Et_2O, washed with saturated solution of $NaHCO_3$ and brine, dried over anh. $MgSO_4$, filtrated, concentrated at rotovap and purified by column chromatography (petroleum ether/ethyl acetate = 5/1) to afford 8.5 mg (51%) of product **7** as colorless oil.

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SUPPLEMENTARY MATERIAL

Supplementary Materials are available electronically from https://www.shd-pub.org.rs/index.php/JSCS/article/view/12460, or from the corresponding authors on request.

И З В О Д

СИНТЕТИЧКА СТУДИЈА АНГУЛАРНИХ ТРИКИНАНА

МИХАИЛО Н. СТЈЕПАНОВИЋ[1], АЛЕКСАНДАР В. ЈАНКОВИЋ[2], БОЈАН З. ВУЛОВИЋ[1], РАДОМИР В. МАТОВИЋ[2] и РАДОМИР Н. САИЧИЋ[1,3]

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Представљена је синтеза ангуларног трикинана, који може послужити као кључни интермедијер за синтезу неколико природних производа (парагинсена, силфинена, сенокисдена). Ситеза се заснива на две узастопне анулације циклопентеновог прстена, код којих су алкени искоришћени као латентне карбонилне функционалне групе (преко Wacker-ове реакције), а анулације циклопентенона су остварене алдолним кондензацијама.

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