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The synthetic potential of α,α-diallylcyrene

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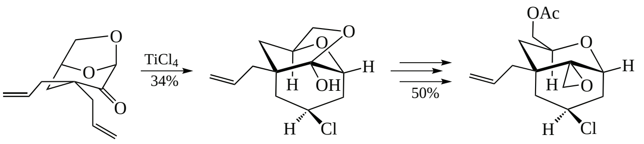
The reaction of cyrene with allyl bromide in THF in the presence of Bu^{t}OK gave the α,α-diallyl derivative of cyrene in 50% yield. This derivative smoothly undergoes iodocyclization on the keto group that is converted into a ketal center to give annulated bis-tetrahydrofuran; intramolecular cationic cyclization in the presence of $SnCl_4$ or $TiCl_4$ results in 2-oxabicyclo[3.3.1]nonan-9-ones. The prospects of using these reactions towards the synthesis of trichothecene sesquiterpenoids modified in the central moiety were assessed.

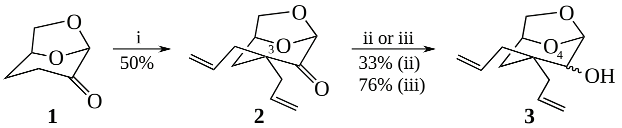


Keywords: cyrene, allyl bromide, intramolecular cationic cyclization, ginkgolides, trichothecene sesquiterpenoids.

Levoglucosenone undergoes the catalytic Diels–Alder reaction with 1,3-dienes to give [4+2]-adducts in good yields and with high stereoselectivity.[1] The reaction with cyclopentadiene affords only two diastereomers of *endo*- (major) and *exo*- (minor) polycycloalkenes.[1(b)–(d)] The presence of a double bond in *R*-hydroxy derivatives of the Diels–Alder adducts between levoglucosenone and butadiene,[2] isoprene[3] and the *R*-hydroxy *endo*-adduct of levoglucosenone and cyclopentadiene allows intramolecular oxa-[1(j)] and carbocyclization reactions to be performed[4] due to the proximity of this bond to the keto group and the acetal center. Moreover, in the latter case, both reactions of intramolecular sequential formation of tetrahydrofuran and cyclohexane rings occur.[4]

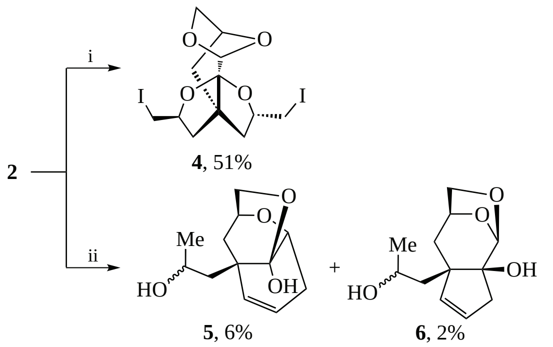
Taking into account the known examples of alkylation of cyrene **1**,[5] incorporation of a more flexible allyl substituent at the α-position to the keto group is sterically attractive in terms of estimating the prospects of intramolecular reactions aimed towards the synthesis of chiral cyclopentanes, substituted tetrahydrofurans, pyrans and cyclopentanes or cyclohexanes. We studied herein the prospects of synthesizing α-allyl derivative of cyrene **1** and some reactions aimed at obtaining the target products noted above. The reaction of allyl bromide and cyrene **1** in the presence of Bu^{t}OK in THF occurs in 50% yield as two competing reactions to give α,α-diallyl derivative **2** and cyrene self-condensation products (Scheme 1). In contrast to the results of the reaction of cyrene with benzyl bromide,[5] monoalkylation products were not found. Attempts to eliminate one of the allyl groups by enolization on treatment with Bu^{t}OK in THF resulted in the destruction of compound **2**, while refluxing in THF in the presence of KH gave alcohols **3**. The possible oxidation of allyl substituents by treatment with O_2 in the presence of $PdCl_2$–CuCl in a DMF–H_2O solution failed since resinification of the reaction mixture occurred, most likely due to the high lability of the resulting trione.

Iodocyclization of compound **2** by treatment with I_2 in the presence of $NaHCO_3$ in acetonitrile occurs as a 5-*exo-trig* attack with intramolecular transformation to bis-tetrahydrofuranylmethyl iodide **4** in 51% yield (Scheme 2). The resulting tetracyclic compound **4** has a *cis*-bound bis-tetrahydrofuran structure that is part of the core of ginkgolides.[6] An alternative reaction includes intramolecular cationic cyclization of diallyl ketone **2**. To preliminarily estimate this option, diallyl ketone **2** was treated with phosphoric acid to afford cyclohexene **5** and cyclopentene **6** (diastereomeric mixture each) in low yields. In both cases, the axial allyl substituent is involved in carbocyclization, and the equatorial substituent is hydroxylated into a secondary alcohol (see Scheme 2). An attempt to perform the Prins reaction under milder conditions using Et_2AlCl[7(a)] resulted in reduction to give the abovementioned (see Scheme 1) diastereomeric alcohols **3** in 76% yield, which is in agreement with the known facts.[7]



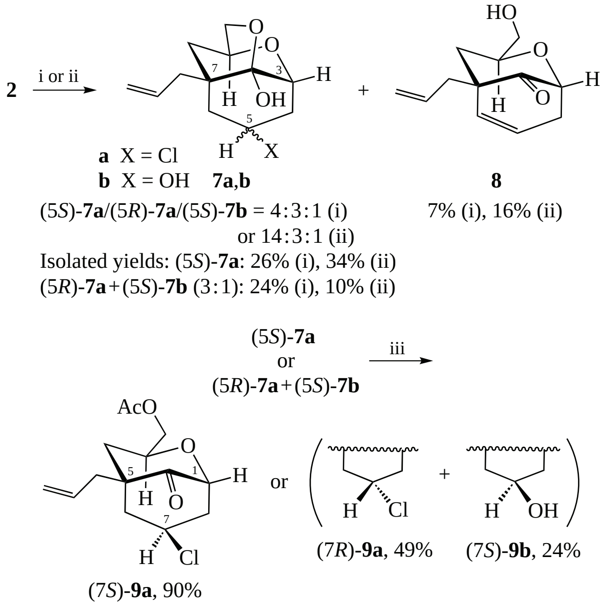
(4*R*)-**3**/(4*S*)-**3** = 6 : 1

Scheme 1 *Reagents and conditions*: i, CH_2=$CHCH_2Br$, Bu^{t}OK, THF, 0→25 °C, 3 h; ii, KH, THF, 70 °C, 15 h; iii, Et_2AlCl, CH_2Cl_2, 25 °C, 2 h.



(2′*R*)-**5**/(2′*S*)-**5** = 4 : 1 (2′*R*)-**6**/(2′*S*)-**6** = 8 : 1

Scheme 2 *Reagents and conditions*: i, I_2, $NaHCO_3$, MeCN, 25 °C, 1 h; ii, H_3PO_4 (85%), 10 days.



a X = Cl
b X = OH **7a**,**b**

8

(5*S*)-**7a**/(5*R*)-**7a**/(5*S*)-**7b** = 4 : 3 : 1 (i)
or 14 : 3 : 1 (ii)
Isolated yields: (5*S*)-**7a**: 26% (i), 34% (ii)
(5*R*)-**7a** + (5*S*)-**7b** (3 : 1): 24% (i), 10% (ii)

7% (i), 16% (ii)

(7*S*)-**9a**, 90%

(7*R*)-**9a**, 49%

(7*S*)-**9b**, 24%

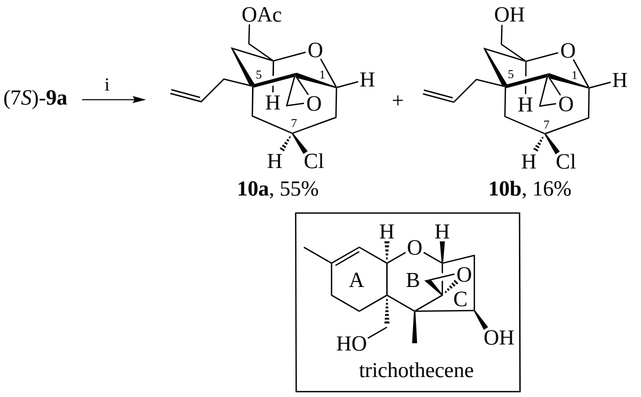
Scheme 3 *Reagents and conditions*: i, SnCl$_4$, MeOH, CH$_2$Cl$_2$, 0→25 °C, 2 h; ii, TiCl$_4$, CH$_2$Cl$_2$, –78→0 °C, 2 h; iii, CH$_2$=C(Me)OAc, TsOH, 25 °C, 15 h; performed separately for (5*S*)-**7a** and (5*R*)-**7a** + (5*S*)-**7b** mixture.

Having studied the extreme conditions of cationic intramolecular cyclization, we began to develop methods for its implementation in the presence of SnCl$_4$ and TiCl$_4$ typically used in such reactions in accordance with reported data.[1(*d*)] Treatment of a solution of diallyl ketone **2** in CH$_2$Cl$_2$ with SnCl$_4$ followed by MeOH[8] gave three products (Scheme 3). Of these, compounds (5*S*)-**7a** and (5*R*)-**7a** were found to be diastereomeric chlorine-containing products of cationic intramolecular cyclization, while compound **8** was a product of deprotonation at the cyclization stage. When TiCl$_4$ is used, the conversion occurs more efficiently and more selectively. In fact, while the yield of chloride (5*S*)-**7a** was 26%, β-chloride (5*S*)-**7a** was obtained in 34% yield in the second case. It should also be noted that in the latter case, the intermediate stage of deprotonation to diene **8** is also more efficient.

We studied the possibility to create an oxirane ring at C-12 in the trichothecene structure aimed[9] at further application of this approach to the synthesis of the bicyclic core of these sesquiterpenoids containing the oxabicyclo[3.3.1]nonane core instead of the oxabicyclo[3.2.1]octane one. To open the oxygen bridge and to simultaneously protect the hydroxy group, β-chloride (5*S*)-**7a** and α-chloride (5*R*)-**7a** as a mixture with alcohol **7b** were treated with isopropenyl acetate in the presence of TsOH (see Scheme 3). After work-up and chromatography, the reaction gave β-chloro acetate (7*S*)-**9a** in 90% yield in the first case, whereas in the second case, α-chloro acetate (7*R*)-**9a** and α-hydroxy acetate (7*S*)-**9b** were isolated in 49 and 24% yields, respectively. At the final stage, subjection of chloro acetate (7*S*)-**9a** to the Corey–Chaykovsky reaction furnished the target epoxy acetate **10a** and epoxy alcohol **10b**, the deacetylation product (Scheme 4). Under similar conditions, chloro acetate (7*R*)-**9a** underwent decomposition to give polar products.

The structure of all new compounds was determined by ^{1}H and ^{13}C NMR spectra using standard HHCosy, HSQC, HMBC, and NOESY two-dimensional correlation techniques and mass spectrometry (for details, see Online Supplementary Materials).

To conclude, α,α-diallyl derivative of cyrene was obtained and its synthetic potential in the synthesis of tetrahydrofuran and cyclohexane derivatives was determined, along with the prospects to access synthetic analogues of trichothecene sesquiterpenoids modified at the tricyclic core, in particular, verrucarol.[9(*i*)]



10a, 55%

10b, 16%

Scheme 4 *Reagents and conditions*: i, Me$_3$S(O)I, NaH, DMSO, 0 °C, 1 h.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.037.

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