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Synthesis of sarcodictyin A analogue containing 14-methyl group and C(12)=C(13) bond in ring A from levoglucosenone

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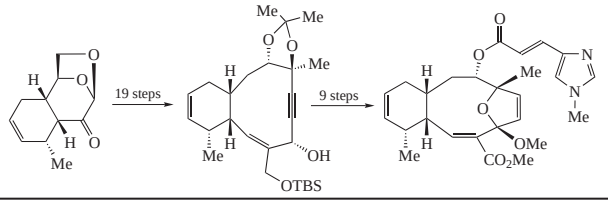
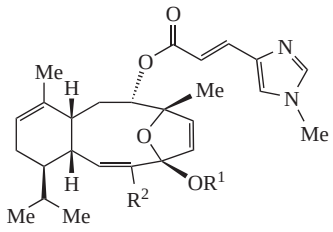
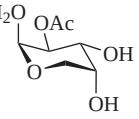
Starting from levoglucosenone piperilene Diels–Alder adduct a total synthesis of sarcodictyin A analogue containing 14-methyl group and C(12)=C(13) bond in ring A was performed, where the key step was the intramolecular cyclization between acetylene and aldehyde moieties to produce a 10-membered carbocycle.



Eleuthesides relate to diterpenoids of '4,7-oxaeunicellane type' having the tricyclic core containing menthane ring *cis*-annelated with a 4,7-oxygen bridged 10-membered cycle.[1] Sarcodictyins A, B and eleutherobin **1**–**3** possess the taxol-like mechanism of cytotoxic action.[2] Obligatory prerequisite for the manifestation of cytotoxic properties in the eleutheside structure is the presence of *N*-methylurocanic acid in the side chain.[3] Howewer, combinatorial sarcodictyin libraries[3] do not take into account the effect of ring A on the biological activity of eleuthesides. Detection of this dependence is perspective to search for available analogous eleuthesides.

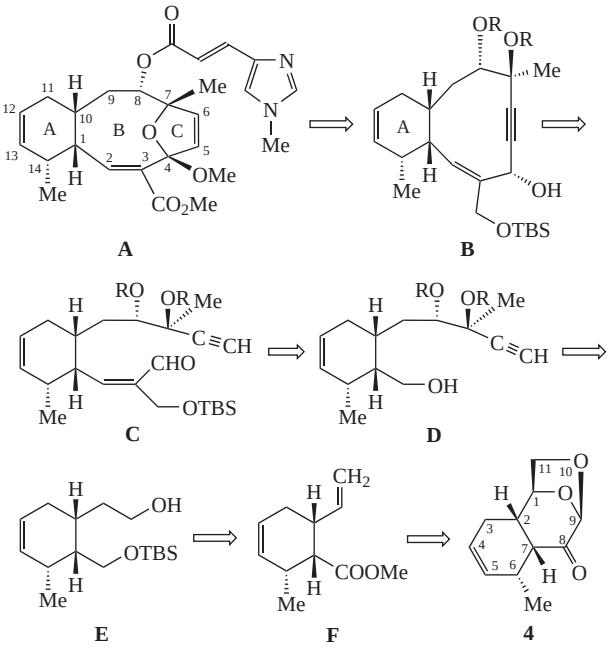


Sarcodictyin A:
1 R^1 = H, R^2 = COOMe
Sarcodictyin B:
2 R^1 = H, R^2 = COOEt
Eleutherobin:
3 R^1 = Me, R^2 = CH_2O

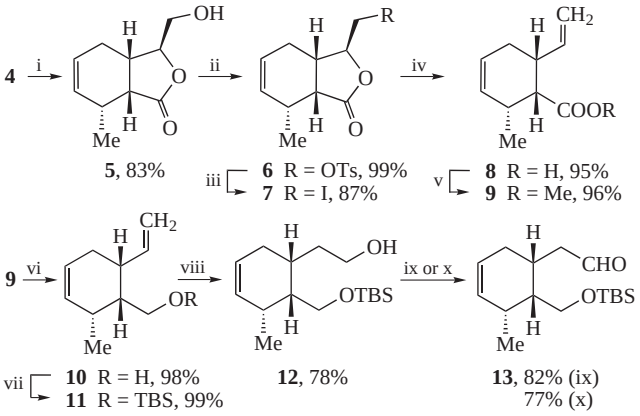


In the synthesis of eleutheside, a convenient starting material is (+)-δ-cadinol[4] isolated from the oleo-resin of Siberian pine *Pinus sibirica* R. Mayr. In our opinion, a suitable starting material for the synthesis of eleutheside analogue with a modified A ring can be a chiral Diels–Alder adduct of levoglucosenone with piperylene.[5] Absolute configuration of C^2, C^6 and C^7 in adduct **4** was identical to the configuration of atoms in the ring A of eleutheside and it has good functionality to build up the side chain. Retrosynthetic Scheme 1 assumes obtaining eleutheside **A** by oxacyclization of carbocyclic derivative **B**, which may be prepared by intramolecular acetylene–aldehyde cyclization of intermediate **C** with the known strategy of eleutheside synthesis.[6] Intermediate **C** can be obtained by construction of side chains in compound **E**, which should be availible from adduct **4**.

To prepare the building block **E** from adduct **4**, we estimated the possibility of C^8–C^9 bond cleavage by Baeyer–Villiger oxidation,[7] which opens the way for the construction of side chains. We have found that treatment of adduct **4** with 30% H_2O_2 in EtOH in the presence of H_2SO_4 gives lactone **5** in 83% yield (Scheme 2). The subsequent tosylation and treatment with NaI afforded iodo



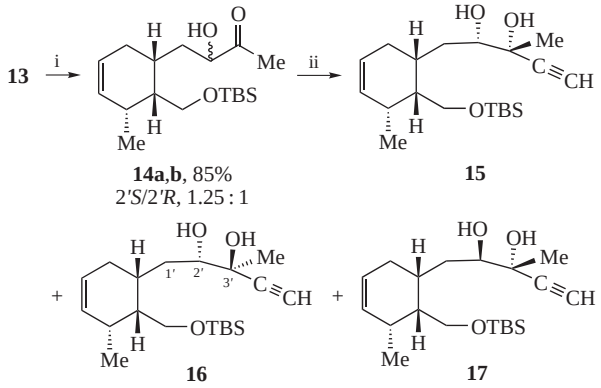
Scheme 1



Scheme 2 *Reagents and conditions*: i, H_2O_2, EtOH, H_2SO_4, 70 °C; ii, *p*-TsCl, Py; iii, NaI, MeCN; iv, Zn, MeOH, AcOH; v, MeI, K_2CO_3, Me_2CO; vi, Bu^i_2AlH, CH_2Cl_2, –78 °C; vii, TBSCl, imidazole, CH_2Cl_2; viii, 9-BBN, THF, then 30% H_2O_2, NaOAc; ix, Py·SO_3, DMSO, Pr^i_2EtN; x, PCC, CH_2Cl_2.

lactone **7**. Mild reduction of compound **7** with zinc in methanol in the presence of acetic acid[8] gave olefinic carboxylic acid **8**. The latter was easily transformed to ester **9** using methyl iodide in the presence of K_2CO_3[9] in a total yield of 65%.

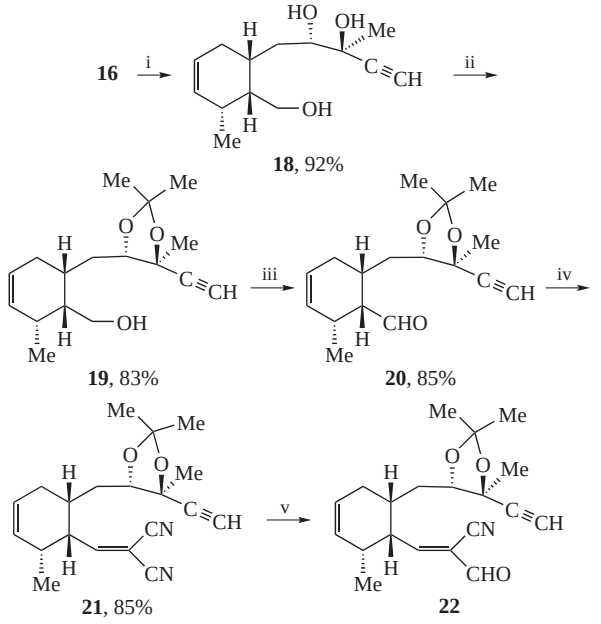
The reduction of ester **9**, followed by protection of hydroxy group in alcohol **10**, led to silyl ether **11**, whose vinyl group was subjected to hydroboration–oxidation to form primary alcohol **12** in 78% yield. Attempted Swern oxidation of alcohol **12** with a view to obtaining aldehyde **13** resulted in a mixture of products which contained no target aldehyde. The oxidation of **12** with Py·SO_3[10] gave aldehyde **13** in 82% yield. The use of more convenient PCC in CH_2Cl_2[11] afforded aldehyde **13** in 77% yield. The overall yield of compound **13** was 40% in nine steps.



Scheme 3 *Reagents and conditions*: i, CH_2=CH(OEt), BuLi, THF, –78 °C, then HCl (pH 3–4), THF, H_2O; ii, HC≡CMgCl, THF, –30 °C.

Aldehyde **13** was reacted with 1-ethoxyvinyllithium (Scheme 3), and subsequent mild hydrolysis of the intermediate enol ether produced a mixture of stereoisomeric hydroxy ketones **14a**,**b** with low selectivity (2′*S*/2′*R* = 1.25; *cf.* ref. 6). 1,2-Addition of ethynylmagnesium chloride to **14a**,**b** mixture gave 43% of **16** in which the configuration of $C^{3'}$ was identical to that of C^7 in the eleutheside core.[1] From the reaction mixture we also isolated isomeric diols **15** and **17** in 6 and 31% yields, respectively.

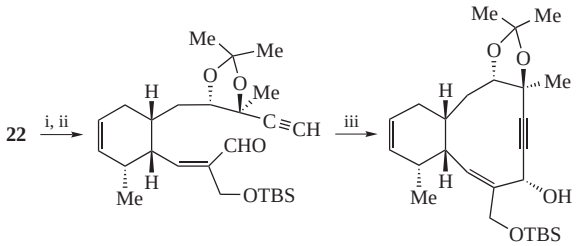
The synthesis was continued by deprotection of TBS-ether **16** with PPTS in MeOH[12] (Scheme 4). The obtained triol **18** was treated with 2,2-dimethoxypropane in the presence of PPTS, and



Scheme 4 *Reagents and conditions*: i, PPTS, MeOH; ii, $Me_2C(OMe)_2$, PPTS, MeOH; iii, PCC, CH_2Cl_2; iv, $CH_2(CN)_2$, β-alanine, EtOH; v, Bu^i_2AlH, CH_2Cl_2, –78°C.

the resulting hydroxy ketal **19** was used for construction of the 'lower' side chain. To avoid possible epimerization at the α-position of aldehyde **20**, the hydroxy group in **19** was oxidized with PCC under mild conditions. The Knoevenagel condensation of aldehyde **20** was carried out with a reactive propanedinitrile. We have discovered that treatment of dinitrile **21** with 2.2 equiv. of Bu^i_2AlH in CH_2Cl_2 initially caused reduction of the *trans*-located cyano group with the formation of nitrile aldehyde **22**. The reduction of dinitrile **21** using 4 equiv. of Bu^i_2AlH aiming at the preparation of dialdehyde resulted in a complex products mixture.

In order to perform the intramolecular acetylene–aldehyde condensation, the *cis*-located cyano group in **22** should be reduced repeatedly. Therewith, the previously formed aldehyde group was converted into an alcohol one which was protected by transforming into TBS-ether (Scheme 5) and next reduction brought about aldehyde **23**. Intramolecular cyclization of **23** by the action of $(Me_3Si)_2NLi$ in THF[6] provided construction of the 10-membered eleutheside core.



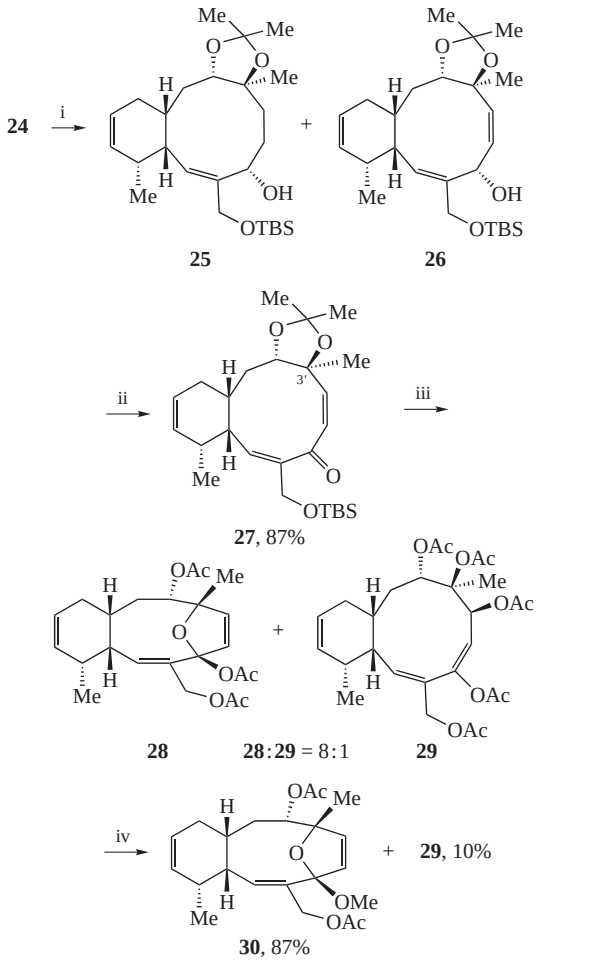
Scheme 5 *Reagents and conditions*: i, Bu^i_2AlH, CH_2Cl_2, –78 °C; ii, TBSCl, imidazole, CH_2Cl_2; iii, $(Me_3Si)_2NLi$, THF.

To complete the formation of the eleutheside core, it was necessary to oxidize the allylic hydroxy group, to hydrogenate the triple bond to the double bond, and to hydrolyze the acetonide protective group.[6]

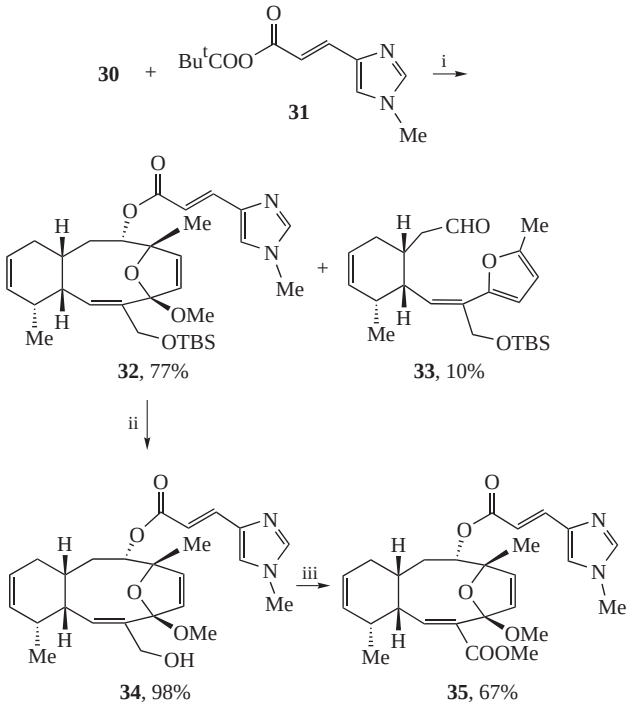
During the Lindlar hydrogenation dienynol **24** was consumed within 6 h to form trienol **26** and the product of its double hydrogenation **25** in a ratio of 2 : 1. A selective hydrogenation of compound **24** to trienol **26** containing only traces of doubly hydrogenated compound **25** was accomplished by fast hydrogenation on 10% Pd/C monitored by TLC (Scheme 6). Trienol **26** was oxidized with Dess–Martin reagent[13] to ketone **27**. The attempts to carry out the oxacyclization of ketone in the course of deprotection from the acetonide group under the action of acidic reagents in MeOH failed. Therefore, the conditions of transfunctionalization of the acetonide into acetates were explored. Reaction of acetonide **27** with TMSOTf in Ac_2O[14] at –10 °C gave an inseparable mixture of triacetate **28** and pentaacetate **29** in a 8 : 1 ratio. The subsequent MeOH solvolysis of the mixture of acetates **28** and **29** in the presence of PPTS afforded methoxy ketal **30** and unreacted pentaacetate **29** (see Scheme 6), which were separated by chromatography.

In going to the final stage of the synthesis of sarcodictyin A analogue, the acetate groups in methoxy ketal **30** were removed by treating with MeONa in methanol to obtain a labile compound. In addition, we have discovered that compounds with the tricyclic eleutheside scaffold lacking a protective group at the atom C^8 decompose with the cleavage of the C^7–C^8 bond. Similar fact was observed when we tried to remove the acetonide protecting group of compound **27**. The first stages of the formation of the desired product were evident, however, the process was ended with decomposition giving complex mixtures containing aldehyde **33** and its blocked derivative (Scheme 7).

Accounting for these complications, the stages of hydrolysis, blocking the primary hydroxy group, and esterification were combined into consecutive operations without isolation of the



Scheme 6 *Reagents and conditions:* i, H_2, Pd–Pb/$CaCO_3$, toluene, **25**:**26** = 1:2, 73% or H_2, 10% Pd/C, toluene, 3 min, **26**, 95%; ii, Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; iii, TMSOTf, Ac_2O, –78 °C → → –10 °C, 84%; iv, PPTS, MeOH.



Scheme 7 *Reagents and conditions:* i, K_2CO_3, MeOH, –10 °C, then TBSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, then **31**, 25 °C; ii, Bu_4NF, THF, 0 °C; iii, Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, then $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, Bu^tOH, H_2O, 0 °C, then CH_2N_2, Et_2O.

intermediate compounds. The hydrolysis of diacetate **30** was carried out under mild conditions by treating with K_2CO_3 in methanol,[15] then the primary hydroxy group was transformed in TBS-ether, and the secondary OH group was esterified with mixed anhydride of *N*-methylurocanic acid[6] **31**. As a result, urocanate **32** was obtained in 77% yield, while the decomposition product **33** was formed in 10% yield only.

The protective *tert*-butyldimethylsilyl group was removed by the treatment of urocanate **32** with Bu_4NF in THF to get alcohol **34**. The oxidation of the hydroxy group in compound **34** with Dess–Martin reagent followed by additional oxidation of the intermediate aldehyde with $NaClO_2$ afforded acid which was esterified with diazomethane. The obtained ester **35** is a real analogue of sarcodictyin A with a methylcyclohexene ring A.

In summary, using the Diels–Alder adduct of levoglucosenone with piperylene as a starting compound we have accomplished a total synthesis of 12,13-dedihydro-14-deisopropyl-11-demethyl-11,12-dihydro-14(*R*)-methyl sarcodictyin A.

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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.2017.03.003.

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