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A study towards the synthesis of (–)-*atrop*-abyssomicin C core•

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Abstract: An attempt to synthesize the cyclohexane core of antibiotic abyssomicin C is described. The initial, protecting group-free approach (relying on internal protection) failed and had to be modified, in order to allow for efficient deprotection of the acid-sensitive cyclization precursor in the penultimate synthetic step. Thus, a pyranoside structural unit was used as a latent lactone/ester functionality, which was deprotected *via* thioacetalization/hydrolysis/oxidation sequence, to give the δ-valerolactone-type cyclization precursor. Unfortunately, the key cyclization reaction was not feasible, even after structural modification of the cyclization precursor. Reluctance towards cyclization turned out to be a general property of (at least some) Δ^7-unsaturated esters, which required the development of a new strategy for this type of transformation.

Keywords: organic synthesis; cyclization; protecting groups; pyranoside; natural products.

INTRODUCTION

Some time ago we embarked on the total synthesis of (–)-*atrop*-abyssomicin C (**1**) – a naturally occurring antibiotic with intricate molecular architecture and a new mechanism of action.[1] Our retrosynthetic analysis, displayed in Scheme 1, relied on incremental topological simplification of the polycyclic target and involved a cyclohexane derivative **2** as a synthetic intermediate. This compound contains 5 stereogenic centers out of 6 carbon atoms (constituting cyclohexane ring; the stereochemistry of the ester-bound carbon atom is irrelevant for the course of synthesis, though), which oriented retrosynthetic analysis of **2** toward stereoselective transforms. In addition, the presence of reactive functional groups required protection: we planned to use internal protection, *i.e.*, to interconnect

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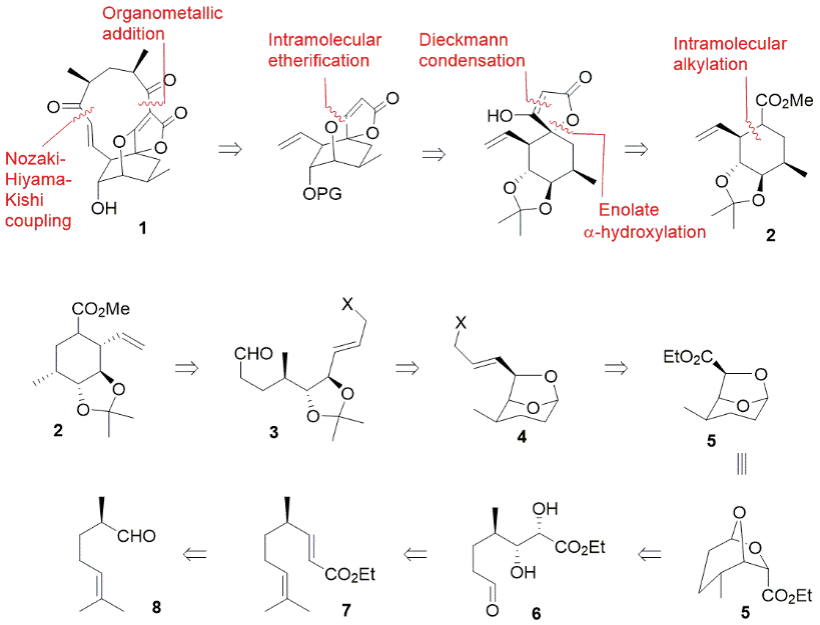
functional groups already present in the molecule, so as to achieve maximum atom-economy (*i.e.*, no introduction of additional atoms, save those constituting the target molecule). This ambition would be accomplished by proceeding *via* intermediate **5**, where vicinal diol and aldehyde functionalities are both present in latent form as bicyclic acetal. Retrosynthetic "hydrolysis" of this compound gives **6**, on its turn obtainable by Sharpless asymmetric dihydroxylation (AD) of diene **7**. Aldehyde **8** (also known as melonal) could be prepared in the optically pure form from geraniol, as previously described (Scheme 2).



Scheme 1. Retrosynthetic analysis of (–)-*atrop*-abyssomicin C.

The synthesis commenced with Sharpless-Katsuki asymmetric epoxidation of geraniol (**9**). Curiously, the optical purity of our product **10** was 85 % (as compared to 95 % *ee* in the literature;[2] we performed the reaction several times, with reproductive results). Reductive opening of epoxide **10** with $NaBH_3CN$,[3] followed by oxidative cleavage of the intermediary diol **11** provided optically enriched (–)--melonal (**8**),[4] which was converted into diene **7** by the Horner–Wadsworth––Emmons modification of the Wittig reaction.[5] Regioselective conversion of this compound into acetal **12** was accomplished by Malaprade–Johnson–Lemieux reaction sequence, with subsequent acetalization.[6] Sharpless asymmetric dihydroxylation of **12** with AD-mix-*β* afforded diol **13**, which was expected to undergo acid-catalyzed cyclization into bicyclic acetal **5**. Upon exposure of **13** to catalytic amounts of *p*-TsOH in chloroform at rt, a monocyclization occurred with the

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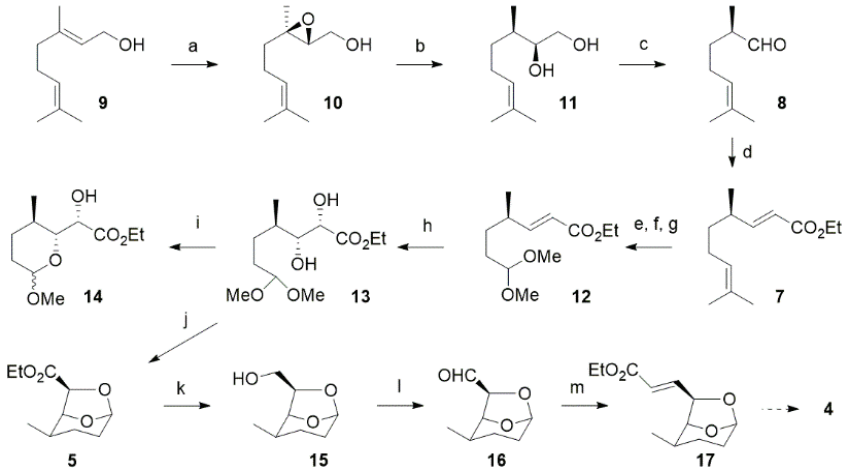
formation of acetal **14** (obtained as an equimolar mixture of stereoisomers). However, performing the reaction at reflux afforded **5** in 62 % yield. The plan called for the conversion of **5** into the allylic intermediate **4**, which would be deprotected (*i.e.*, **4** → **3**) to allow for cyclization. We were aware that the deprotection might be non-trivial so, before continuing along the path leading to **4**, we examined the acid-catalyzed deprotection of its structurally simpler predecessor **5**. Indeed, the compound turned out to be capricious toward deprotection (as we feared), as no reaction was observed with methanol, under Lewis, or protic, acid-catalyzed conditions. This was a bad predicament, as the allylic derivative of type **4** was supposed to be more sensitive to acid-catalyzed side-reactions, with respect to **5**. In addition, aldehyde **16** was difficult to purify (aldehydes with an oxygen substituent at the α-position are often hydrated and trail at TLC and silica column). Also, Wittig olefination of aldehyde **16** proceeded sluggishly and (in addition to the desired product **17**) afforded an unidentified side product. For all these reasons, we modified the initial plan and decided to proceed *via* monocyclic acetal **14**, where the loss in atom-economy would be compensated by better control of reactivity.



Scheme 2. Reagents and conditions: a) $Ti(OiPr)_4$, (–)-DET, *t*-BuOOH, ms 4Å, CH_2Cl_2, –20 °C; b) $NaCNBH_3$, $BF_3{\cdot}Et_2O$, THF; c) $NaIO_4$, SiO_2, H_2O, CH_2Cl_2; d) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF; e) OsO_4 (cat.), NMO, *t*-BuOH, H_2O, 87 %; f) $NaIO_4$, MeOH, H_2O, 89 %; g) $CeCl_3{\cdot}7H_2O$, $HC(OMe)_3$, 87 %; h) $(DHQD)_2PHAL$, OsO_4, AD-mix-β, $MsNH_2$, *t*-BuOH, H_2O, 0 °C, 81 %; i) *p*-TsOH (cat), $CHCl_3$, rt, 94 %; j) *p*-TsOH (cat), $CHCl_3$, reflux, 62 %; k) $LiAlH_4$, THF, rt, 88 %; l) DMP, CH_2Cl_2, rt; m) $Ph_3P{:}CHCO_2Et$, CH_2Cl_2, rt, 35 %. DET = diethyl tartrate; NMO = *N*-methylmorpholine *N*-oxide; $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether; *p*-TsOH = *para* toluenesulfonic acid.

After the secondary hydroxyl group in **14** was protected as TBS-ether, we tested (on the model compound **18**) the conditions for the conversion of the cyclic acetal into the corresponding lactone **19**. Here again, compound **18** proved reluc-

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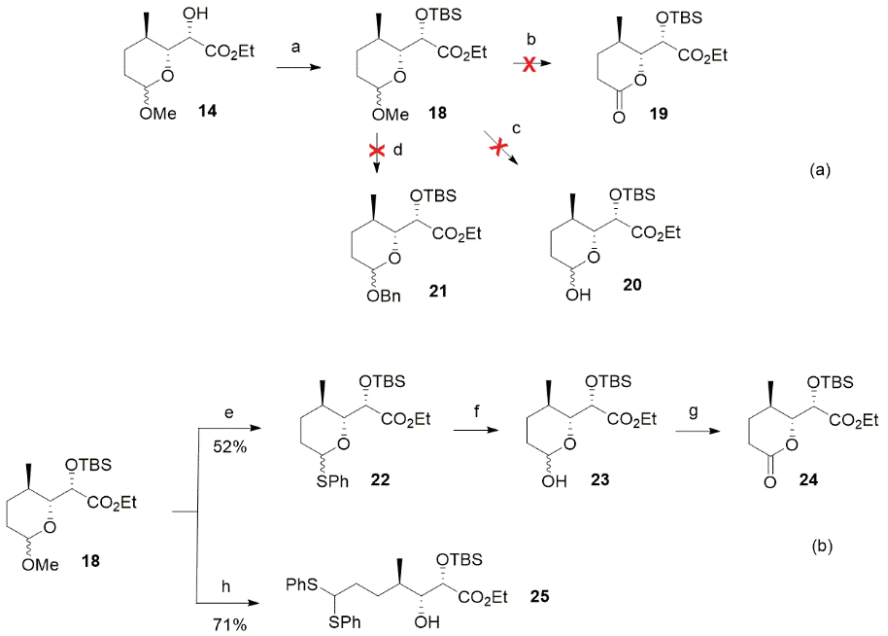
tant towards Jones oxidation (to **19**), hydrolysis (to **20**),[7] or alkoxy-group exchange (to **21**; Scheme 3, part a). Therefore, a two-step maneuver was applied, comprising the conversion of **18** into monothioacetal **22**, followed by its deprotection into hemiacetal **23** (Scheme 3, part b). Our initial attempt to catalyze the first reaction (**18** → **22**) with $LiClO_4$ failed;[8] however, using equimolar amount of $TiCl_4$ at low temperature provided **22** in 52 % yield.[9] Upon exposure to $Hg(ClO_4)_2$,[10] monothioacetal **22** was instantaneously converted into hemiacetal **23** (73 %). This result indicated that the deprotection of the advanced synthetic intermediate should be feasible under the similar reaction conditions. Interestingly, with two equivalents of thiophenol, acetal **18** was smoothly converted into dithioacetal **25** (71 %).



Scheme 3. Reagents and conditions: a) TBSOTf, 2,4,6-collidine, CH_2Cl_2, 0 °C, 94 %; b) Jones reagent; c) H_2O, DME, reflux; d) *p*-methoxybenzyl alcohol, *p*-TsOH (cat.), ms 4Å, $CHCl_3$, rt; e) PhSH (1 eq), $TiCl_4$, $CHCl_3$, –20 °C→rt, 52 %; f) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, rt, 73 %; g) Jones reagent; h) PhSH (2 eq), $TiCl_4$, $CHCl_3$, –20 °C→rt, 71 %. TBSOTf = *t*-butyldimethylsilyl trifluoromethanesulfonate; ms = molecular sieves; DME = dimethoxyethane.

An attempt to obtain aldehyde **27** by direct, low-temperature (–78 °C) reduction of ester **18** with DIBALH was not successful, as the alcohol **26** was formed immediately (Scheme 4). Therefore, ester **18** was first reduced to alcohol **26** (DIBALH, 81 %), then oxidized to aldehyde **27** by DMP (92 %). Wittig reaction with **27** proceeded without event (93 %), providing the conjugated ester **28** which was further reduced to allylic alcohol **29** (DIBALH, 82 %) and converted into mesylate **30** (81 %) via sulfene.[11] The conversion of acetal **30** into lactone

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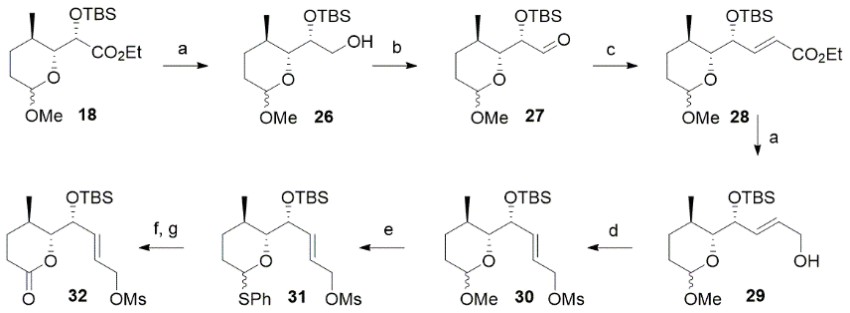
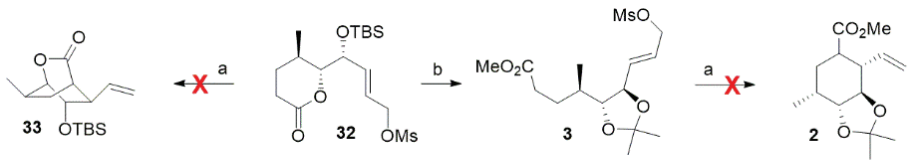
32 was accomplished *via* a previously developed protocol (*i.e.*, **18** → **22** → **23** → **24**) in 23 % overall yield, thus setting up the stage for the pivotal cyclization reaction (*i.e.*, **32** → **33**).



Scheme 4. Reagents and conditions: a) DIBALH, Et_2O, –40 °C, 81 % (for **26**); 82 % (for **29**); b) DMP, CH_2Cl_2, rt, 92 %; c) Ph_3P:$CHCO_2Et$, CH_2Cl_2, rt, 93 %; d) MsCl, Et_3N, CH_2Cl_2, -20 °C, 81 %; e) PhSH (1 eq), $TiCl_4$, $CHCl_3$, –15 °C, 46 %; f) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, –15 °C; g) Jones reagent, 62 % from **31**. DIBALH = diisobutylaluminum hydride; DMP = Dess–Martin periodinane; MsCl = methanesulfonyl chloride.

The cyclization was attempted with LDA as a base, in the presence of HMPA, at –78 °C (Scheme 5). Unfortunately, no reaction was observed, neither at –78 °C, nor at rt. When the temperature was raised to 65 °C, the starting material decomposed (Scheme 5). We reasoned that the strain increase associated with the formation of a bridged bicyclic system might have hampered the reaction. In that case, the cyclization would be facilitated if a condensed, rather than bicyclic, system would be closed. Therefore, we exposed lactone **32** to the action of 2,2-dimethoxypropane, methanol and catalytic amount of CSA,[12] to convert it into ester **3** – hopefully a superior cyclization precursor. Surprisingly, in this reaction an unfavorable equilibrium was established, and we were not able to shift it in favor of the desired compound **3**, even with a considerable excess of 2,2-dimethoxypropane. However, we isolated enough of **3** for the cyclization trial. This experiment was performed under the same reaction conditions as attempted cyclization of **32**, unfortunately with the identical result.



Scheme 5. Reagents and conditions: a) LDA, THF, HMPA, –78 °C → 65 °C; b) 2,2-dimethoxypropane, CSA (cat.), MeOH, rt, 26 % (brsm). HMPA = hexamethylphosphoramide; CSA = camphorsulfonic acid.

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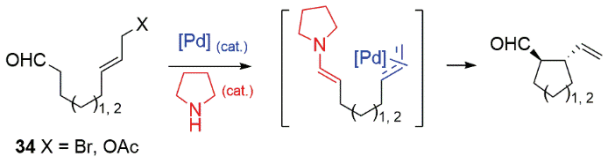
Subsequent study showed that, quite surprisingly, esters containing allylic (pseudo)halide moiety are not good substrates for the 6-membered ring closure, and we had to find another way to effect the related 6-*exo*-cyclization and prepare synthetic equivalent of **2**. The solution was found in the development of double-catalyzed cyclization, where synergistic action of both pyrrolidine and organotransition metal catalyst on aldehydes of type **34** resulted in 5-, or 6-membered ring closure. The newly developed method has general synthetic applicability and it has eventually allowed us to accomplish the total synthesis of (–)--*atrop*-abyssomicin C.[13] However, that study is above the scope of this paper and has been described elsewhere.[14]



Scheme 6. Ring closure by double catalysis.

EXPERIMENTAL

General experimental details

All chromatographic separations were performed on Silica (SDS, 60 Å, 40–63 μm). Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on a Bruker Avance III 500 (^{1}H-NMR at 500 MHz, ^{13}C-NMR at 125 MHz), a Bruker Avance III 300 (^{1}H-NMR at 300 MHz, ^{13}C-NMR at 75 MHz) and a Varian Gemini 200, (^{1}H-NMR at 200 MHz, ^{13}C-NMR at 50 MHz). Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (J) are in Hz.

Compounds **10**[2] and **11**[3] were prepared according to literature procedures.

Ethyl (*R,E*)-4,8-dimethylnona-2,7-dienoate (**7**) was obtained from (*R*)-melonal, using the procedure described in the literature for another compound.[5] Starting from 3.04 g of melonal, 1.326 g (88 %) of compound **7** was obtained as a colorless oil.

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

*Ethyl (*R,E*)-7,7-dimethoxy-4-methylhept-2-enoate (**12**)*

A) Dihydroxylation of compound **7**: A mixture of diene **7** (1.36 g; 6.47 mmol), OsO_4 (1.3 mL of 0.1 M solution in *t*-BuOH; 0.13 mmol), NMO (0.555 mL of 60 % solution in H_2O; 3.235 mmol), *t*-BuOH (27 mL) and H_2O (13.5 mL) was stirred at rt. After 20 min additional NMO (0.555 mL of 60 % solution in H_2O; 3.235 mmol) was added. After 4 h (as the reaction was not complete) additional OsO_4 (0.5 mL of 0.1 M solution in *t*-BuOH; 0.05 mmol) was added and the reaction mixture was stirred for an additional 5 h. The reaction was quenched by the addition of celite (500 mg), H_2O (7 mL) and $NaHSO_3$ (1 mL of 37.5 % aqueous solution), stirred for 15 min, filtered, extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated at rotavap, to afford 1.5 g of the crude product. Purification by dry-flash chromatography (SiO_2; eluent: heptane/EtOAc = 1/1, followed by pure EtOAc) afforded 1.38 g (87 %) of the product as colorless oil.

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B) Oxidative fragmentation of the diol: A solution of the product from the previous step (1.38 g) in MeOH (70 mL) was added to the solution of $NaIO_4$ (4.23 g) in H_2O (45mL), with stirring. After 2 min precipitation occurred, and after 6 min TLC indicated the completion of the reaction. The reaction mixture was diluted with CH_2Cl_2 and H_2O, extracted with CH_2Cl_2, washed with H_2O, dried over anh. $MgSO_4$ and concentrated at rotavap to afford 925 mg (89 %) of the crude aldehyde which was used in the next step without purification.

C) Acetalization of the aldehyde: The crude product from the previous step (870 mg) was treated with $CeCl_3 \cdot 7H_2O$ (122 mg), $HC(OMe)_3$ (5 g; 5.16 ml) and MeOH (12 mL), according to the literature procedure,[6] to give 948 mg (87 %) of the title compound **12** as colorless oil.

*Ethyl (2*S*,3*R*,4*R*)-2,3-dihydroxy-7,7-dimethoxy-4-methylheptanoate (**13**)*

Compound **13**: dihydroxylation of compound **12** was accomplished according to the modified literature procedure;[13] the modification consists in increasing the quantities of OsO_4 and the chiral ligand ($(DHQD)_2PHAL$), as the reaction with the commercial AD-mix is too slow. Thus, a mixture of compound **12** (795 mg), $(DHQD)_2PHAL$ (161 mg), OsO_4 (1.73 mL of the 0.1 M solution in *t*-BuOH), AD-mix-β (4.83 g), methanesulfonamide (328 mg), *t*-BuOH (15.5 mL) and H_2O (17.3 mL) was stirred at 0 °C for 11.5 h. Work-up as described in the literature procedure, followed by purification of the crude product by dry-flash chromatography (SiO_2; gradient elution by heptane/EtOAc = 3/1 → 1/1) afforded 730 mg (81 %) of the title compound **13**, as a colorless oil (a mixture of isomers in 3.7:1 ratio).

*Ethyl (2*S*)-2-hydroxy-2-((2*R*,3*R*)-6-methoxy-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (**14**)*

Compound **14**: a solution of compound 13 (200 mg; 0.757 mmol) and *p*-TsOH (1 mg) in $CHCl_3$ (5 mL) was stirred at rt for 1 h 15 min. Solid K_2CO_3 was added to the reaction mixture, followed by H_2O. Extraction with $CHCl_3$, followed by drying over anh. $MgSO_4$ and concentration at reduced pressure gave 166 mg (94 %) of the title compound **14** as a colorless oil (a nearly equimolar mixture of isomers).

*Ethyl (1*S*,2*R*,5*S*,7*S*)-2-methyl-6,8-dioxabicyclo[3.2.1]octane-7-carboxylate (**5**)*

Compound **5**: a solution of compound **13** (60 mg; 0.23 mmol) and *p*-TsOH (7.7 mg; 0.04 mmol) in $CHCl_3$ (6 mL) was heated to reflux for 8 h. After cooling to rt, solid K_2CO_3 was added, followed by aqueous solution of K_2CO_3 and H_2O. The reaction mixture was extracted with $CHCl_3$, washed with water, dried over anh. Na_2SO_4 and concentrated under reduced pressure, to afford 43 mg of the crude product. Purification by flash-chromatography (SiO_2; eluent: heptane/Et_2O = 3/2) afforded 28 mg (62 %) of the title compound **5**, as a colorless oil (a mixture of isomers in 2.5:1 ratio).

*((1*S*,2*R*,5*S*,7*R*)-2-methyl-6,8-dioxabicyclo[3.2.1]octan-7-yl)methanol (**15**)*

Compound **15**: a mixture of compound **5** (26 mg; 0.13 mmol), $LiAlH_4$ (7 mg; 0.184 mmol) and THF (1 mL) was stirred, initially at 0 °C, then at rt, until TLC indicated the complete conversion. A usual work-up afforded 18 mg (88 %) of the title compound **15**, as a colorless oil (a mixture of isomers in 2.8:1 ratio).

*(Ethyl (*E*)-3-((1*S*,2*R*,5*R*,7*R*)-2-methyl-6,8-dioxabicyclo[3.2.1]octan-7-yl)acrylate (**17**)*

A) Oxidation of alcohol **15** to aldehyde **16**: A mixture of compound **15** (18 mg; 0.114 mmol), DMP (144.8 mg; 0.34 mmol) and CH_2Cl_2 (1 mL) was stirred at rt for 1 h. Standard work-up, followed by flash-chromatography (SiO_2; eluent: heptane/EtOAc = 2/1) afforded 6 mg (33 %) of the title compound **16**. Note: the aldehyde is hydrated and does not have a well-

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defined Rf value at TLC plates: with *n*-heptane/EtOAc = 3/1, *Rf* = 0.1–0.25; with *n*-heptane/EtOAc = 1/1, *Rf* = 0.2–0.4. Aldehyde **16** was immediately used for the next step.

B) Wittig reaction with aldehyde **16**: a mixture of aldehyde **16** (6 mg; 0.0384 mmol; from the previous step) and ethoxycarbonylmethylene triphenylphosphorane (67 mg; 0.192 mmol; 5 equiv.) in CH_2Cl_2 (0.5 mL) was stirred overnight. Standard work-up, followed by purification by flash chromatography (SiO_2; eluent: *n*-heptane/EtOAc = 12/1) afforded 3 mg (35 %) of the title compound **17** (equimolar mixture of stereoisomers), as a colorless oil (an equimolar mixture of isomers).

Ethyl (*2S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*2R,3R*)-6-methoxy-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (**18**) was prepared from compound **14**, applying the procedure described in the literature.[15] Starting from 152 mg of **14**, 213 mg (94 %) of compound **18** was obtained, as a colorless oil (a mixture of isomers in 1.5:1 ratio).

*Attempts to convert compound **18** into compounds **19**, **20** and **21***

Attempt to convert compound **18** into lactone **19** was done according to the literature procedure.[16] TLC monitoring indicated a very slow reaction with substantial decomposition of starting material.

Attempt to convert compound **18** into hemiacetal **20** was performed according to the literature procedure.[17] No reaction was observed, and the starting material was recovered unchanged.

Attempt to convert compound **18** into compound **21**: a mixture of compound **18** (10 mg; 0.029 mmol), *p*-methoxybenzyl alcohol (8 mg; 0.058 mmol), *p*-TsOH (1 mg), molecular sieves (4 Å) and $CHCl_3$ (0.3 mL) was stirred at rt. No reaction could be observed after 2 h. After 24 h slow formation of 2 products was observed.

Ethyl (*2S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*2R,3R*)-3-methyl-6-(phenylthio)tetrahydro-2*H*-pyan-2-yl)acetate (**22**) was prepared according to the modified literature procedure:[9] the modification is in that 1 equiv. of $TiCl_4$ was used (instead of 10 mol. %, as described in the reference). Starting from 11 mg of compound **18**, after purification by dry-flash chromatography (SiO_2; eluent: *n*-heptane/EtOAc = 18/1), 7 mg (52 %) of compound **22** was obtained, as a colorless oil (a mixture of isomers in 5: 1 ratio).

Ethyl (*2S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-((*2R,3R*)-6-hydroxy-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (**23**) was prepared according to literature procedure.[10a] The reaction is immediate, however, the reaction mixture was left additional 45 min at r.t. to verify the stability of the product under the reaction conditions. The crude product was dissolved in minimum quantity of CH_2Cl_2, this solution was diluted with the same amount of *n*-heptane and applied to the SiO_2 column for dry-flash purification (eluent: *n*-heptane/EtOAc = 4/1) to afford 4 mg (73 %) of the title compound **23** which spontaneously crystallizes (a mixture of isomers in 2: 1 ratio).

Ethyl (*2S,3R,4R*)-2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-4-methyl-7,7-bis(phenylthio)heptanoate (**25**): A solution of compound **18** (10 mg; 0.029 mmol), thiophenol (0.06 mL of 1 M solution in $CHCl_3$; 0.06 mmol) and $TiCl_4$ (0.03 mL of 1 M solution in $CHCl_3$; 0.03 mmol) in $CHCl_3$ (0.3 mL) was stirred at –15 °C. After 2 h additional thiophenol (0.03 mL of 1 M solution in $CHCl_3$; 0.03 mmol) was added and the reaction mixture was allowed to reach rt with stirring, for 3 h. Standard work-up, followed by purification by dry-flash chromatography (SiO_2; gradient elution with: *n*-heptane/EtOAc = 12/1 → 9/1) afforded 11 mg (71 %) of the title compound **25**, as a viscous oil.

(*2R*)-2-((*Tert*-butyldimethylsilyl)oxy)-2-((*2R,3R*)-6-methoxy-3-methyltetrahydro-*2H*-pyran-2-yl)ethan-1-ol (**26**): DIBALH (6.4 mL of 1.5 M solution in toluene; 9.6 mmol; 4 equiv.) was added over 10 min to a cold (–40 °C) solution of compound **18** (840 mg; 2.424 mmol) in

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Et_2O (25 mL). The reaction is virtually instantaneous. The reaction mixture was diluted with a mixture of concentrated aqueous solution of Rochelle's salt and Et_2O, stirred for 1 h at rt, extracted with ether, dried over anh. $MgSO_4$, concentrated at rotavap and purified by flash chromatography (SiO_2, eluent: *n*-heptane/EtOAc = 5/1) to give 600 mg (81 %) of the title compound **26**, which spontaneously crystallizes (a mixture of isomers in 1.4:1 ratio).

(*2S*)-2-((*Tert*-butyldimethylsilyl)oxy)-2-((*2R,3R*)-6-methoxy-3-methyltetrahydro-2*H*-pyran-2-yl)acetaldehyde (**27**): a mixture of compound **26** (110 mg; 0.36 mmol) and DMP (300 mg; 0.71 mmol) in CH_2Cl_2 (7 mL) was stirred at rt for 1 h. Work-up as described in the literature[18] afforded 100 mg (92 %) of the title compound **27** as a colorless oil (an equimolar mixture of isomers).

Ethyl (*4R,E*)-4-((*tert*-butyldimethylsilyl)oxy)-4-((*2R,3R*)-6-methoxy-3-methyltetrahydro-*2H*-pyran-2-yl)but-2-enoate (**28**): a solution of compound **27** (100 mg; 0.33 mmol) and ethoxycarbonyl triphenylphosphorane (244 mg; 0.7 mmol) in CH_2Cl_2 (5 mL) was stirred at rt. After 40 h, additional phosphorane reagent (120 mg) was added, and stirring was continued for 47 more hours. The reaction mixture was concentrated at rotavap, dissolved in EtOH (5 mL), $NaBH_4$ (3 mg) was added and the mixture was stirred for 15 min at rt, followed by addition of aqueous solution of NH_4Cl and CH_2Cl_2. The organic extract was washed with water, dried over anh. $MgSO_4$, concentrated at rotavap and purified by flash chromatography (SiO_2, eluent: *n*-heptane/EtOAc = 12/1) to give 115 mg (93 %) of the title compound **28**, as a colorless oil (a mixture of (*E*)-isomers in 1.4: 1 ratio, with 10 % of (*Z*)-isomers).

(*4R,E*)-4-((*Tert*-butyldimethylsilyl)oxy)-4-((*2R,3R*)-6-methoxy-3-methyltetrahydro-*2H*-pyran-2-yl)but-2-en-1-ol (**29**) was obtained according to the procedure described for the preparation of compound **26** (above). Starting from 365 mg (0.981 mmol) of compound **28**, 315 mg of the crude product **29** was obtained. Purification by flash chromatography (SiO_2; gradient elution with: *n*-heptane/EtOAc = 5/1 → 3/1) afforded 265 mg (82 %) of the title compound **29**, as a colorless oil. A fraction of pure (*Z*)-isomers was isolated (less polar than (*E*)-isomers) and separately characterized by NMR.

(*4R,E*)-4-((*Tert*-butyldimethylsilyl)oxy)-4-((*2R,3R*)-6-methoxy-3-methyltetrahydro-2*H*-pyran-2-yl)but-2-en-1-yl methanesulfonate (**30**): the mesylation of compound **29** was accomplished according to the literature procedure.[11] Starting from 68 mg (0.206 mmol) of compound **29**, 68 mg (81 %) of the title compound **30** was obtained as colorless oil (a mixture of isomers in 1.3:1 ratio).

(*4R,E*)-4-((*Tert*-butyldimethylsilyl)oxy)-4-((*2R,3R*)-3-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-2-yl)but-2-en-1-yl methanesulfonate (**31**): a solution of compound **30** (35 mg; 0.086 mmol), thiophenol (0.086 mL of 1 M solution in $CHCl_3$; 0.086 mmol) and $TiCl_4$ (0.086 mL of 1 M solution in $CHCl_3$; 0.086 mmol) in $CHCl_3$ (1 mL) was stirred at –20 to -15 °C, for 30 min. The reaction mixture was diluted with water and $CHCl_3$, the organic extract was washed with H_2O, dried over anh. $MgSO_4$, concentrated and purified by flash chromatography (SiO_2; eluent: *n*-heptane/EtOAc = 5/1) to give 19 mg (46 %) of the title compound **31**, as a viscous oil (a mixture of isomers in 5:1 ratio).

*(*R,E*)-4-((Tert-butyldimethylsilyl)oxy)-4-((2*R,*3*R*)-3-methyl-6-oxotetrahydro-2*H*-pyran-2-yl)-but-2-en-1-yl methanesulfonate (**32**)*

A) The conversion of compound **31** into the corresponding hemiacetal was accomplished according to the procedure described for the preparation of compound **23** (see above), starting from 133 mg (0.27 mmol) of compound **31**. The crude hemiacetal was used in the next step without purification.

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B) Oxidation of hemiacetal to lactone **32**: A solution of the product from the previous step in acetone (28 mL) was treated with a solution of Jones reagent (1 mL of 2.7 M solution; 2.7 mmol) at 0 °C. The reaction is instantaneous. Standard work-up afforded 110 mg of the crude product **32**. The product is unstable in contact with SiO_2, so the purification was accomplished by very fast dry flash chromatography (13 g SiO_2; gradient elution with: 12×10 mL of *n*-heptane/EtOAc = 2/1, followed by 12×10 mL of *n*-heptane/EtOAc = 1/1), to afford 67 mg (62 % over 2 steps) of the title compound **32** as a colorless oil.

Attempted cyclization of compound **32** (attempted synthesis of **33**): a solution of compound **31** (35 mg; 0.089 mmol) in THF (0.3 mL) was added dropwise to a cold (–78 °C) solution of LDA (0.1 mmol) in THF (1 mL), with stirring under an argon atmosphere. As no reaction was observed at TLC, HMPA (72 mg; 0.070 mL; 0.4 mmol) was added, and the reaction mixture was allowed to reach rt with stirring. As no reaction was observed by TLC, the reaction mixture was heated to 65 °C; after 30 min, TLC indicated total decomposition of the starting product, without any well-defined product.

Methyl (*R*)-4-((*4R,5R*)-2,2-dimethyl-5-((*E*)-3-((methylsulfonyl)oxy)prop-1-en-1-yl)-1,3-dioxolan-4-yl)pentanoate (**3**): a solution of compound **32** (35 mg; 0.089 mmol), 2,2-dimethoxypropane (0.4 mL), MeOH (6 mg; 0.078 mL; 0.19 mmol) and camphorsulfonic acid (CSA, 12 mg; 0.054 mmol) was stirred at rt. As the conversion was very slow (according to TLC), additional CSA (8 mg), 2,2-dimethoxypropane (0.2 mL) and MeOH (0.01 mL) were added and the reaction was stirred for 2 h. Although the reaction was not complete, TLC indicated the formation of degradation products, so the reaction was interrupted. Work-up as described previously,[12] afforded 35 mg of the crude product. Purification by flash chromatography afforded 4 mg (26 %, based on the recovered starting compound) of the title compound **3** (less polar), followed by 18 mg of the unreacted, recovered starting compound **32**.

Attempted cyclization of compound **3** (attempted synthesis of **2**): this attempt was performed as described for the attempted synthesis of compound **33** (see above), with the same result.

ИЗВОД

СТУДИЈА СИНТЕЗЕ ЦИКЛОХЕКСАНСКОГ ЈЕЗГРА АНТИБИОТИКА (–)-*атрој*-АБИСОМИЦИНА С

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У раду је описан покушај синтезе циклохексанског језгра антибиотика абисомицина С. Иницијални покушај, да се овај задатак оствари без коришћења заштитних група (коришћењем интерне заштите), морао је бити модификован, како би се обезбедила ефикасна депротекција циклизационог прекурсора у претпоследњем кораку синтезе. Стога је као латентни синтетички еквивалент естарске, односно лактонске функционалне групе коришћен дериват пиранозида, чија је депротекција у дериват δ-валеролактона извршена секвенцом: тиоацеталицација/хидролиза/оксидација. Нажалост, кључна реакција циклизације није остварена, чак ни са структурно модификованим прекурсором. Показало се да су Δ^7-незасићени естри изненађујуће лоши супстрати за циклизацију, што нас је подстакло на развој нове стратегије која би омогућила овај тип трансформације.

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