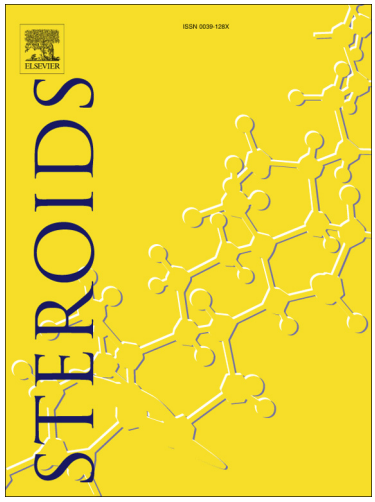

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Enantioselective catalytic approach to the C23-C28 subunit of 24α-methyl steroids

Viktoryia S. Yakimchyk[a], Volha V. Kazlova[a], Alaksiej L. Hurski[a,*], Rimma G. Savchenko[b], Svetlana A. Kostyleva[b], Vladimir N. Zhabinskii[a], Vladimir A. Khripach[a]

[a]*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str., 5/2, 220141 Minsk, Belarus*

[b]*Institute of Petrochemistry and Catalysis of Russian Academy of Sciences, prosp. Oktyabrya 141, 450075 Ufa, Russian Federation*

Enantioselective synthesis of C23-C28 subunit of campestane steroids based on catalytic methods is reported. The synthesis was started from (S)-2-isopropyl-4-nitrobutan-1-ol, which is easily accessible by the reaction between isovaleraldehyde and nitroethylene catalyzed by only 2% of (S)-trimethylsilyldiphenylprolinol. Removal of one "extra" carbon from the nitroalcohol was achieved by Ni-catalyzed hydrodecarboxylation of the redox-active ester intermediate. The synthesized C23-C28 fragment was attached to a steroidal core by Julia-Kocienski reaction of a steroidal aldehyde with metallated C23-C28 sulfone. The obtained product of olefination was easily transformed to a precursor of campesterol and (Z)-22-dehydrocampesterol.

Keywords: Michael addition; Decarbonylation; Ni-catalyzed decarboxylation; Campesterol; cis-22-Dehydrocampesterol.

Abbreviations: DEAD, diethyl azodicarboxylate; DIC, diisopropyl carbodiimide; DMAP, 4-dimethylaminopyridine; DPPA, diphenylphosphoryl azide; HMDS, hexamethyldisilazane; LiHMDS, lithium hexamethyldisilazide; NHPI, *N*-hydroxyphthalimide; PE, petroleum ether; TBDPSCl, *tert*-butyldiphenylsilyl chloride

* Corresponding author. *E-mail address:* ahurski@iboch.by (A. Hurski)

1 Introduction

Steroids bearing a 24α-methyl substituent in the side chain are known as campestanes and typically they are produced by plants and marine organisms. The most abundant steroid of this group is campesterol (**1**), an important component of the plant cell membrane [1] (Fig. 1). Crinosterol (**2**) differing from campesterol by the presence of a Δ^{22}-double bond was found in marine invertebrates [2]. Several campestanes are remarkable for their potent biological activity. For instance, brassinolide (**3**) and related phytohormones regulate biological processes in plants at low nanomolar concentrations [3, 4]. Ecdysteroid makisterone A (**4**) is a moulting hormone of the honey bee, *Apis mellifera* [5]. Recently, new cytotoxic sterols swinhoeisterols, bearing the campestane side chain along with a unique rearranged skeleton were isolated from the sponge *Theonella swinhoei* [6, 7]. Swinhoeisterol A (**5**) shows an inhibitory activity (IC_{50} = 2.9 μM) against h(p300), a histone acetyltransferase associated with the manifestation of cancer.

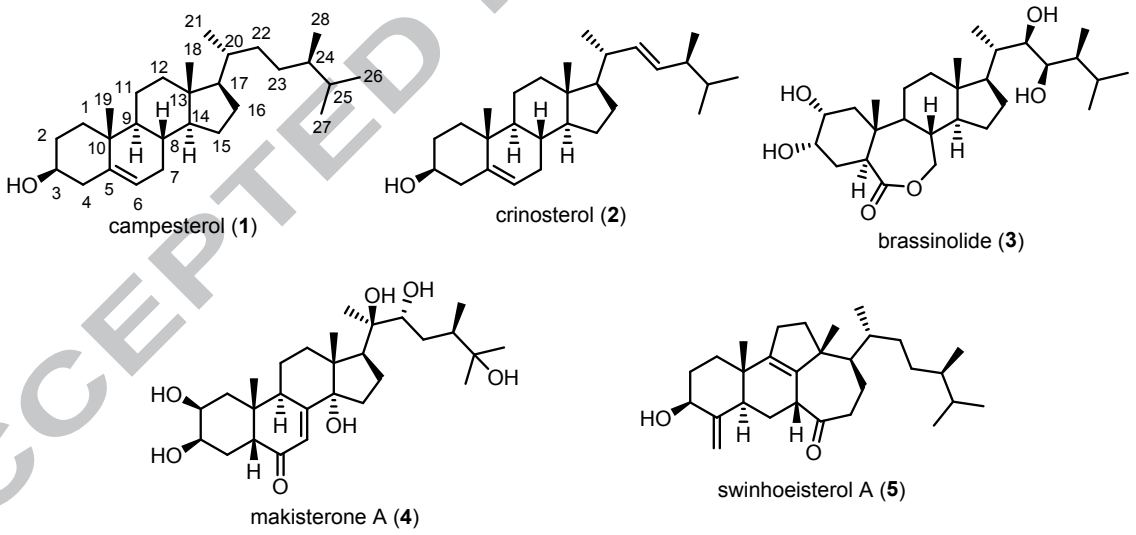


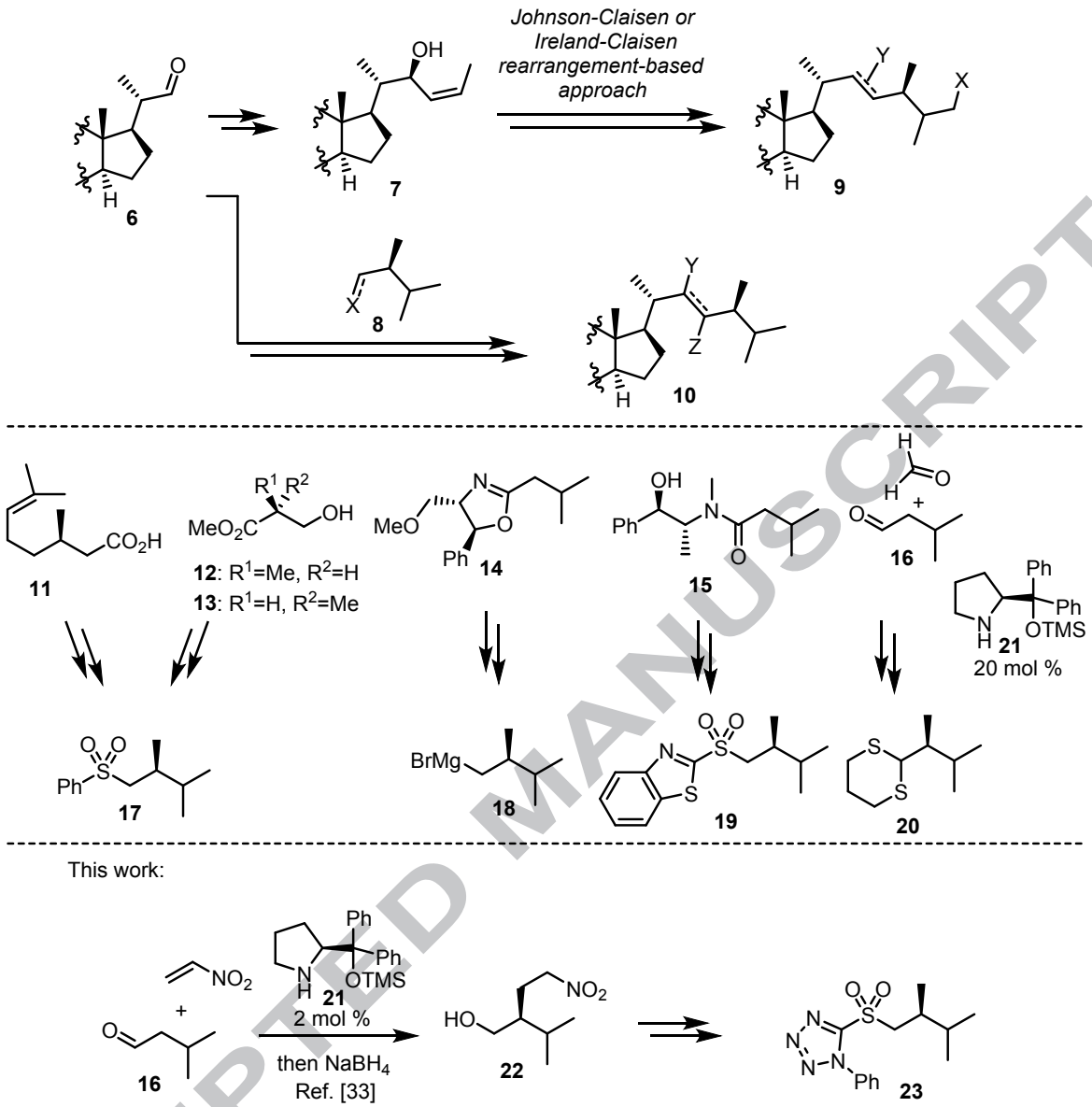
Fig. 1. Structures of some natural steroids with a campestane side chain

In synthesis of campestanes, the side chain is always constructed synthetically because steroids bearing a 24α-methyl group are still not available as starting materials in a pure form. Generally, two strategies are used for the formation of the side chain (Scheme 1). One of them is based on a sequence of diastereoselective reactions [8-15], which in most cases includes Johnson-Claisen or Ireland-Claisen reaction of allylic alcohol **7** [8-14] (or similar ones [15]). Alternatively, the target

molecule can be obtained by attaching a chiral side chain to a steroidal core. As far as steroidal C22 aldehydes **6** are easily accessible, their coupling with C23-C28 fragments is the most frequently applied method of the convergent synthesis of campestanes.

To prepare C23-C28 units, either modification of the chiral commercial starting material [16-22] or asymmetric methods of synthesis [23-29] were previously used. Mori reported preparation of sulfone **17** starting from commercial (*R*)-(+)-citronellic acid (**11**) [16]. In our laboratory, the same sulfone was obtained from chiral Roche esters **12** and **13** [18, 19]. Alkylation of chiral auxiliary-modified intermediates **14** and **15** was used in synthesis of organomagnesium reagent **18** [30] and benzothiazole derivative **19** [31]. Although these approaches are efficient, they suffer from an important disadvantage in that they require the use of stoichiometric amounts of a chiral starting material or an auxiliary, which is not ideal from the standpoint of atom economy.

With the idea of the need of more "green" way to the C23-C28 unit of campestanes, we have recently developed an asymmetric organocatalytic hydroxymethylation-based method of synthesis of dithiane **20** [32]. Although the key step in this approach is catalytic and the method is suitable for preparation of multigram quantities of the product, it is not optimal because the required amount of the chiral catalyst of 20% is relatively high. A more efficient way to the C23-C28 fragment is still demanded. In this article, we report preparation of subunit **23** based on dehomologation of optically pure nitro alcohol **22**, which is available *via* an asymmetric reaction catalyzed by only 2% of chiral organocatalyst **21** and proceeding with more than 99% enantioselectivity [33].



Scheme 1. Approaches to the synthesis of campestane side chains **9, 10** and C23-C28 fragments **17-20**, **23**

2 Experimental

2.1 General

Melting points were measured using a Boetius apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AVANCE 500 (Bruker Biospin, Rheinstetten, Germany) spectrometer operating at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C. Chemical shift values are given in δ (ppm) relative to the residual solvent peaks: δ_H 7.26 and δ_C 77.16 for $CDCl_3$, and coupling constants are reported in Hz. COSY, HSQC, HMBC, and NOESY experiments were carried out with the use of the standard Bruker program package. HRMS/MS-spectra were acquired with an Agilent 6550 iFunnel QTOF (Agilent Technologies, USA). Chemicals were purchased from Aldrich and Fluka and used as received. Optical rotations were measured with an Autopol III polarimeter. Solvents were dried and freshly distilled according to standard procedures [34]. (*S*)-2-Isopropyl-4-nitrobutan-1-ol (**22**) was prepared in a 78% yield from 3-methylbutanal (**16**) and nitroethylene in the presence of 2% of (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**21**) and 20% of *m*-nitrobenzoic acid according to the procedure described in [33]. All reactions were performed under positive argon pressure. TLC was performed on precoated aluminum backed TLC sheets (silica gel 60 F254) and visualized by spraying with phosphomolybdic acid followed by heating. Column chromatography was conducted with Merck silica gel 60: 70–230 mesh.

2.2 Chemical synthesis

*2.2.1 (S)-tert-Butyl(2-isopropyl-4-nitrobutoxy)diphenylsilane (**22a**)*

A solution of (*S*)-2-isopropyl-4-nitrobutan-1-ol (**22**) (6.0 g, 37.2 mmol) and imidazole (10.1 g, 148 mmol) in DMF (75 mL) was kept under argon at ambient temperature for 12 h. Then it was cooled to 0 °C and treated with water (75 mL). The mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 94:6) to give **22a** (10.2 g, 68%) as a colorless oily liquid. $[\alpha]_D^{20}$ = -2.09 (c 1.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.67 – 7.63 (m, 4H), 7.47 – 7.38

(m, 6H), 4.48 – 4.33 (m, 2H), 3.64 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.59 (dd, *J* = 10.5, 6.5 Hz, 1H), 2.20 – 2.10 (m, 1H), 2.07 – 1.98 (m, 1H), 1.81 – 1.71 (m, 1H), 1.45 – 1.36 (tt, *J* = 9.4, 4.8 Hz, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 135.7 (x 4), 133.5, 133.4, 129.97, 129.95, 127.9 (x 4), 74.9, 64.8, 44.0, 28.9, 27.3, 27.0 (x 3), 20.0, 19.5, 19.3. HRMS (ESI$^+$): calcd for $C_{23}H_{33}NNaO_3Si$ $[M+Na]^+$ 422.2122, found 422.2119.

*2.2.2 (S)-3-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-methylpentanal (**24**)*

A mixture of **22a** (304 mg, 0.76 mmol), K_2CO_3 (168 mg, 1.22 mmol) and methanol (5.4 mL) was stirred at 0 °C under argon for 1 h. After this, a freshly prepared solution of $KMnO_4$ (80.6 mg, 0.51 mmol) and $MgSO_4$ (67.6 mg, 0.56 mmol) in water (3.2 mL) was added dropwise. Stirring was continued at 0 °C for 3 h, then the mixture was filtered through a pad of silica gel and evaporated. The residue was dissolved in EtOAc, washed with water until neutral and dried (Na_2SO_4). Solvents were evaporated and the residue was chromatographed on SiO_2 (PE-EtOAc, 95:5) to give aldehyde **24** (234 mg, 84%) as a colorless oily liquid. $[\alpha]_D^{20}$ = 5.01 (c 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.79 (dd, *J* = 2.6, 2.0 Hz, 1H), 7.69 – 7.62 (m, 4H), 7.47 – 7.37 (m, 6H), 3.67 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.55 (dd, *J* = 10.2, 7.7 Hz, 1H), 2.47 (ddd, *J* = 16.3, 8.1, 2.8 Hz, 1H), 2.40 (ddd, *J* = 16.3, 4.9, 1.8 Hz, 1H), 2.15 – 2.07 (m, 1H), 1.82 – 1.72 (m, *J* = 13.6, 6.8 Hz, 1H), 1.05 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 203.2, 135.7 (x 4), 133.5 (x 2), 129.8 (x 2), 127.8 (x 4), 65.4, 43.9, 42.4, 28.6, 26.9 (x 3), 20.3, 19.5, 19.3. HRMS (ESI$^+$): calcd for $C_{23}H_{32}NaO_2Si$ $[M+Na]^+$ 391.2064, found 391.2058.

*2.2.3 (S)-tert-Butyl(2,3-dimethylbutoxy)diphenylsilane (**25**)*

A solution of the aldehyde **24** (729 mg, 1.99 mmol) and $(Ph_3P)_3RhCl$ (184 mg, 0.20 mmol) in toluene was thoroughly purged with argon for 15 min. The temperature was brought up to 100 °C, after which a solution of DPPA (546 mg, 1.99 mmol) in toluene (2.2 mL) was added over 4 h. The reaction mixture was stirred for another 1 h, then the solvent was evaporated *in vacuo*, and the residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 99:1) to give silane **25** (558 mg, 83%) as a colorless oily liquid. $[\alpha]_D^{20}$ = 4.14 (c 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.72 – 7.68 (m, 4H), 7.46 – 7.38 (m, 6H), 3.60 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.51 (dd, *J* = 9.9, 6.6 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.57 (dp, *J* = 13.0, 6.7 Hz, 1H), 1.08 (s, 9H), 0.89 (d, *J* = 4.0 Hz,

3H), 0.88 (d, *J* = 4.0 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ ^{13}C NMR ($CDCl_3$) δ 135.8 (x 4), 134.3, 134.3, 129.6 (x 2), 127.7 (x 4), 67.5, 41.6, 28.9, 27.0 (x 3), 20.9, 19.5, 18.3, 12.9. HRMS (APCI): calcd for $C_{22}H_{33}OSi$ $[M+H]^+$ 341.2295, found 341.2294.

*2.2.4 (S)-2-Isopropyl-4-nitrobutyl benzoate (**26**)*

To a solution of (*S*)-2-isopropyl-4-nitrobutan-1-ol (**22**) (10.3 g, 64 mmol) in pyridine (64 mL), DMAP (78 mg, 0.64 mmol) and benzoyl chloride (11.0 mL, 95 mmol) were added at 0 °C. The mixture was stirred for 1 h, then the cooling bath was removed and stirring was continued at ambient temperature for additional 12 h. After addition of water (250 mL) and separation of the organic layer, the water phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with 5% HCl, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 92:8) to give nitro benzoate **26** (13.1 g, 78 %) as viscous yellow oil. $[\alpha]_D^{20}$ = -6.95 (c 0.777, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.05 – 7.99 (m, 2H), 7.62 – 7.53 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 4.58 – 4.47 (m, 2H), 4.41 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.24 (dd, *J* = 11.5, 6.5 Hz, 1H), 2.25 (dtd, *J* = 14.7, 7.8, 4.7 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.88 (pd, *J* = 7.0, 5.0 Hz, 1H), 1.76 (ddq, *J* = 9.5, 6.5, 4.8 Hz, 1H), 1.01 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 166.6, 133.3, 130.0, 129.7 (x 2), 128.7 (x 2), 74.4, 65.6, 40.9, 29.3, 27.3, 19.7, 19.4. HRMS (APCI): calcd for $C_{14}H_{20}NO_4$ $[M+H]^+$ 266.1387, found 266.1342.

*2.2.5 (S)-3-((Benzoyloxy)methyl)-4-methylpentanoic acid (**27**)*

A mixture of nitro benzoate **26** (12.91 g, 48.7 mmol), $NaNO_2$ (14.0 g, 203 mmol), AcOH (28 mL) and DMSO (97 mL) was stirred at 50 °C for 4 h. Then it was cooled to ambient temperature and diluted with 10% HCl. The product was extracted with EtOAc (5 x 30 mL). The combined extracts were washed with water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 90:10) to give 9.82 g (80%) of acid **27** as viscous yellow oil. $[\alpha]_D^{20}$ = -7.66 (c 0.783, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 4.43 (dd, *J* = 11.1, 5.0 Hz, 1H), 4.25 (dd, *J* = 11.1, 7.3 Hz, 1H), 2.50 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.41 (dd, *J* = 15.9, 8.2 Hz, 1H), 2.34 – 2.25 (m, 1H), 1.89 (dd, *J* = 12.2, 6.6 Hz, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ 179.00, 166.67, 133.11, 130.24, 129.70 (x 2), 128.51 (x 2), 66.00, 40.43, 34.15, 29.04, 19.71, 19.65. HRMS (ESI^+): calcd for $C_{14}H_{18}NaO_4$ $[M+Na]^+$ 273.1097, found 273.1101.

*2.2.6 (S)-4-((1,3-Dioxoisoindolin-2-yl)oxy)-2-isopropyl-4-oxobutyl benzoate (**28**)*

Diisopropyl carbodiimide (4.7 mL, 30 mmol) was added to a cooled to 0 °C mixture of the acid **27** (6.26 g, 25 mmol), *N*-hydroxyphthalimide (4.5 g, 27.6 mmol), DMAP (150 mg, 1.2 mmol) and dry CH_2Cl_2 (125 mL). The cooling bath was removed and the mixture was stirred at ambient temperature for 3 h. Then solvents were evaporated under reduced pressure and the residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 80:20) to give NHPI ester **28** (9.69 g, 98%) as viscous yellow oil. $[\alpha]_D^{20}$ = -11.29 (c 0.797, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.07 – 8.03 (m, 2H), 7.91 – 7.85 (m, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.59 – 7.53 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.26 (s, 1H), 4.51 (dd, *J* = 11.4, 5.1 Hz, 1H), 4.37 (dd, *J* = 11.4, 6.8 Hz, 1H), 2.84 (d, *J* = 6.7 Hz, 2H), 2.43 – 2.34 (m, 1H), 2.01 (ddd, *J* = 13.8, 12.1, 6.4 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 169.2 (x 2), 166.6, 162.0, 134.9 (x 2), 133.2, 130.2, 129.8 (x 2), 129.1, 128.6 (x 2), 124.1 (x 2), 65.1, 40.9, 31.2, 29.0, 19.9, 19.5. HRMS (ESI^+): calcd for $C_{22}H_{21}NO_6$ $[M+Na]^+$ 418.1259, found 418.1261.

*2.2.7 (S)-2,3-Dimethylbutyl benzoate (**29**)*

A flask was charged with $NiCl_2{\bullet}6H_2O$ (0.051 g, 0.215 mmol) and 4,7-diphenyl-1,10-phenanthroline (0.142 g, 0.427 mmol), and the apparatus was purged with Ar. DMF (2.2 mL, anhydrous) was added, and the mixture was stirred for 10 minutes. THF (9 mL) and *i*-PrOH (1.1 mL) were then added, followed by a solution of **28** (0.841 g, 2.127 mmol) in 1.6 ml of THF and Zn powder (0.070 g, 1.070 mmol). Immediately following the addition of the Zn powder, $PhSiH_3$ (neat, 0.786 mL, 6.381 mmol) was added dropwise. Upon completion of the addition of $PhSiH_3$, the reaction mixture was placed in a preheated 40 °C oil bath and stirred for 1 hour. After 1 hour the mixture was allowed to cool to ambient temperature and 30 ml of half-saturated solution of NH_4Cl was added. The organic layer was separated, the aqueous was extracted with EtOAc (4 x

10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 98:2) to give ester **29** (206 mg, 47 %) as a colorless oil. $[\alpha]_D^{20}$ = 6.55 (c 0.327, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.08 – 8.01 (m, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 4.29 (dd, *J* = 10.8, 5.8 Hz, 1H), 4.16 (dd, *J* = 10.8, 6.8 Hz, 1H), 1.88 – 1.72 (m, 2H), (0.98 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H)), 0.92 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 166.9, 132.9, 130.7, 129.7 (x 2), 128.5 (x 2), 68.5, 38.4, 29.7, 20.5, 18.6, 13.4.

*2.2.8 (S)-5-((2,3-Dimethylbutyl)thio)-1-phenyl-1H-tetrazole (**32**)*

A mixture of the benzoate **29** (1.070 g, 5.19 mmol), KOH (436 mg, 7.77 mmol) and MeOH (3 mL) was stirred at 50 °C for 3 h. After cooling to ambient temperature, the mixture was diluted with water (9 mL) and extracted with a mixture Et_2O-pentane (1:1, 4 x 5 mL). The combined organic phases were dried over Na_2SO_4 and the resulting solution was concentrated by distillation under normal pressure. The residue containing (*S*)-2,3-dimethylbutan-1-ol (**30**) was diluted with THF (50 mL), and then triphenylphosphine (1.496 g, 5.70 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (**31**) (1.016 g, 5.70 mmol) were added. The mixture was cooled to 0 °C, and then a solution of DEAD in toluene (40 wt %, 2.6 mL, 5.97 mmol) was added dropwise. After the entire reagent has been added, the reaction mixture was warmed to room temperature and stirred for 12 h. Then it was concentrated under reduced pressure, the resulting residue was diluted with a mixture of petroleum ether and ethyl acetate (9:1, 90 mL). The precipitate was filtered off and the resulting filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on SiO_2 (PE-EtOAc, 100:0 ⇒ 95:5) to give phenyl tetrazole **32** (1.292 g, 95% based on **29**) as a colorless oil. $[\alpha]_D^{20}$ = 16.33 (c 0.307, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 5H), 3.51 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.22 (dd, *J* = 12.6, 8.3 Hz, 1H), 1.84 – 1.71 (m, 2H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 154.9, 133.9, 130.2, 129.9 (x 2), 124.0 (x 2), 38.7, 38.6, 31.5, 20.4, 17.8, 15.1. HRMS (ESI^+): calcd for $C_{13}H_{18}N_4S$ $[M+H]^+$ 263.1327, found 263.1325.

*2.2.9 (S)-5-((2,3-Dimethylbutyl)sulfonyl)-1-phenyl-1H-tetrazole (**23**)*

A mixture of sulphide **32** (1.24 g, 4.73 mmol), $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$ (584 mg, 0.47 mmol), H_2O_2 (30%, 2.84 mL, 25 mmol) and EtOH (24 mL) was stirred at ambient temperature for 48 h. Then it was diluted with water (75 mL) and extracted with Et_2O (4 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on SiO_2 (PE-EtOAc, 100:0 ⇒ 92:8) to give sulfone **23** (1.332 g, 96%) as viscous colourless oil. $[\alpha]_D^{20}$ = 4.82 (c 0.250, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.71 – 7.63 (m, 2H), 7.66 – 7.55 (m, 3H), 3.84 (dd, *J* = 14.4, 3.7 Hz, 1H), 3.52 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.27 (dddd, *J* = 13.6, 8.5, 7.0, 3.9 Hz, 1H), 1.84 (pd, *J* = 6.8, 4.2 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 2H), 0.90 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 154.2, 133.2, 131.6, 129.8 (x 2), 125.3 (x 2), 60.1, 33.3, 32.5, 19.4, 17.8, 15.8. HRMS (ESI^+): calcd for $C_{13}H_{18}N_4NaO_2S$ $[M+Na]^+$ 317.1043, found 317.1043.

*2.2.10 (22Z,24S)-6β-Methoxy-24-methyl-3α,5-cyclo-5α-cholest-22-ene (**34**)*

A freshly prepared solution of LiHMDS (prepared by addition of 0.91 M BuLi (0.66 mL, 0.60 mmol) to a solution of HMDS (0.13 mL, 0.62 mmol) in THF (0.62 mL) was added dropwise under argon at -55 °C to a solution of sulfone **23** (176 mg, 0.60 mmol) in THF (1.2 mL). After stirring the reaction mixture at this temperature for 70 min, a solution of the aldehyde **33** (103 mg, 0.30 mmol, prepared according to [35, 36]) in THF (0.60 mL) was added. The mixture was stirred at -55 °C for 1 h, then the cooling bath was removed and the mixture was kept overnight at ambient temperature. Water (270 μL) was added, and after stirring for 1 h, the mixture was diluted with EtOAc (10 mL) and washed with water (10 mL). After separating the organic layer, the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was chromatographed on SiO_2 (PE-EtOAc, 98:2) to give olefin **34** (64 mg, 52%) as a colorless oil, containing about 4% of the corresponding 22*E*-isomer (measured by the ratio of signals at 5.06 (m, 1H, 22*Z*-isomer), 4.98 (t, 1H, 22*Z*-isomer) and 5.16 (m, 2H, 22*E*-isomer)). The product was crystallized from methanol to give white crystals with mp 86-

88 °C, containing about 1% of the 22*E*-isomer. $[\alpha]_D^{20}$ = 27.4 (c 0.543, $CHCl_3$). NMR data are summarized in Table 1. HRMS (APCI): calcd for $C_{29}H_{49}O$ $[M+H]^+$ 413.3778, found 413.3773.

*2.2.11 (24R)-6β-Methoxy-24-methyl-3α,5-cyclo-5α-cholestane (**35**)*

A mixture of olefin **34** (24.6 mg, 60 μmol), PtO_2 (12.3 mg, 50% w/w), EtOAc (700 μL) and EtOH (1160 μL) was hydrogenated under atmospheric pressure at room temperature until .the ·necessary quantity of hydrogen was absorbed. After completion of the reaction, the mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification of the crude product by flash chromatography on silica gel (PE-EtOAc, 98:2) afforded campestane **35** (21 mg, 82%) as an oil. $[\alpha]_D^{20}$ = 48.3 (c 0.697, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.32 (s, 3H), 2.77 (t, *J* = 2.8 Hz, 1H), 1.99 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.89 (dt, *J* = 13.4, 2.9 Hz, 1H), 1.02 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 1.8 Hz, 3H), 0.64 (dd, *J* = 5.0, 3.8 Hz, 1H), 0.43 (dd, *J* = 8.0, 5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 82.6, 56.7 (x 2), 56.5, 48.2, 43.5, 42.9, 40.5, 39.0, 36.1, 35.5, 35.2, 33.8, 33.5, 32.6, 30.6, 30.5, 28.5, 25.1, 24.3, 22.9, 21.7, 20.4, 19.4, 18.8, 18.4, 15.5, 13.2, 12.4. HRMS (APCI): calcd for $C_{29}H_{50}O$ $[M+H]^+$ 415.3934, found 415.3935.

*2.2.12 (22Z,24S)-24-Methylcholesta-5,22-dien-3β-ol (**36**) /cis-22-dehydrocampesterol (**36**)/*

A mixture of **34** (25 mg, 61 μmol), $TsOH•H_2O$ (2.7 mg, 14 μmol), dioxane (2.7 mL) and water (0.9 mL) was stirred at at 75 °C for 4 h. Then solvents were evaporated, the residue was dissolved in EtOAc (10 mL) and washed with water (5 mL). The water layer was extracted with EtOAc (3 × 3 mL). The combined organic phases were dried over Na_2SO_4, and evaporated. The residue was chromatographed on SiO_2 (PE-EtOAc, 85:15 ⇒ 80:20) to give sterol **36** (21 mg, 87%) as white crystals. $[\alpha]_D^{20}$ = -60.7 (c 0.257, $CHCl_3$). Mp 161-163 °C (methanol). NMR data are summarized in Table 1. HRMS (APCI): calcd for $C_{28}H_{47}O$ $[M+H]^+$ 399.3621, found 399.3598; calcd for $C_{28}H_{45}$ $[M+H-H_2O]^+$ 381.3516, found 381.3517.

Table 1 – ^{1}H and ^{13}C NMR spectroscopic data for compounds **34** and **36**[a,b,c]

Position	Compound

	ether **34**		*cis*-22-dehydrocampesterol (**36**)	
	δ, C	δ, H	δ, C	δ, H
1	33.5	1.50 (m, 1H) / 0.86 (m, 1H)	37.4	1.85 (m, 1H) / 1.08 (m, 1H)
2	25.1	1.74 (m, 1H) /1.52 (m, 1H)	31.8	1.84 (m, 1H) / 1.52 (m, 1H)
3	21.7	0.88 (m, 1H)	71.9	3.52 tt (11.2, 4.7)
4	13.2	0.65 (t, *J* = 4.3 Hz, 1H) /0.43 (dd, *J* = 7.9, 5.1 Hz, 1H)	42.45	2.28 (m, 1H) / 2.23 (m, 1H)
5	35.4	-	140.9	-
6	82.6	2.77 (t, *J* = 2.5, 1H)	121.8	5.35 (m, 1H)
7	35.2	1.89 (dt, *J* = 13.5, 2.9 Hz, 1H) /1.05 (m, 1H)	32.0	1.97 (m, 1H)/1.53 (m, 1H)
8	30.7	1.71 (m, 1H)	32.1	1.44 (m, 1H)
9	48.3	0.81 (m, 1H)	50.3	0.93 (m, 1H)
10	42.8		36.7	
11	22.9	1.41 (m, 2H)	21.2	1.51 (m, 1H) / 1.45 (m, 1H)
12	40.4	1.97 (dt, *J* = 12.5, 3.2 Hz, 1H) / 1.16 (m, 1H)	39.9	1.99 (m, 1H) / 1.19 (m, 1H)
13	43.5	-	42.38	-
14	56.8	1.04 (m, 1H)	57.0	1.01 (m, 1H)
15	24.3	1.56 (m, 1H) / 1.11 (m, 1H)	24.4	1.54 (m, 1H) / 1.03 (m, 1H)
16	28.6	1.67 (m, 1H) / 1.13 (m, 1H)	28.5	1.69 (m, 1H) / 1.14 (m, 1H)
17	56.3	1.13 (m, 1H)	56.1	1.12 (m, 1H)
18	12.7	0.75 (s, 3H)	12.3	0.72 (s, 3H)
19	19.5	1.03 (s, 3H)	19.6	1.01 (s, 3H)
20	34.7	2.39 (m, 1H)	34.6	2.39 (m, 1H)
21	20.7	0.95 (d, *J* = 6.5 Hz, 3H)	20.7	0.96 (d, *J* = 6.5 Hz, 3H)
22	131.3	4.97 (t, *J* = 10.6 Hz, 1H)	131.3	4.98 (t, *J* = 10.6 Hz, 1H)
23	135.5	5.06 (t, *J* = 10.5 Hz, 1H)	135.4	5.06 (t, *J* = 10.5 Hz, 1H)
24	38.4	2.21 (m, 1H)	38.5	2.20 (m, 1H)
25	33.5	1.39 (m, 1H)	33.5	1.40 (m, 1H)
26	20.1	0.83 (d, *J* = 6.7 Hz, 3H)	20.1	0.83 (d, *J* = 6.8 Hz, 3H)
27	20.5	0.88 (d, *J* = 6.7 Hz, 3H)	20.5	0.87 (d, *J* = 6.7 Hz, 3H)
28	18.8	0.91 (d, *J* = 6.7 Hz, 3H)	18.8	0.91 (d, *J* = 6.7 Hz, 3H)
OMe	56.7	3.32 (s, 3H)		

[a] NMR chemical shifts (δ) are from spectra obtained in $CDCl_3$ solutions.

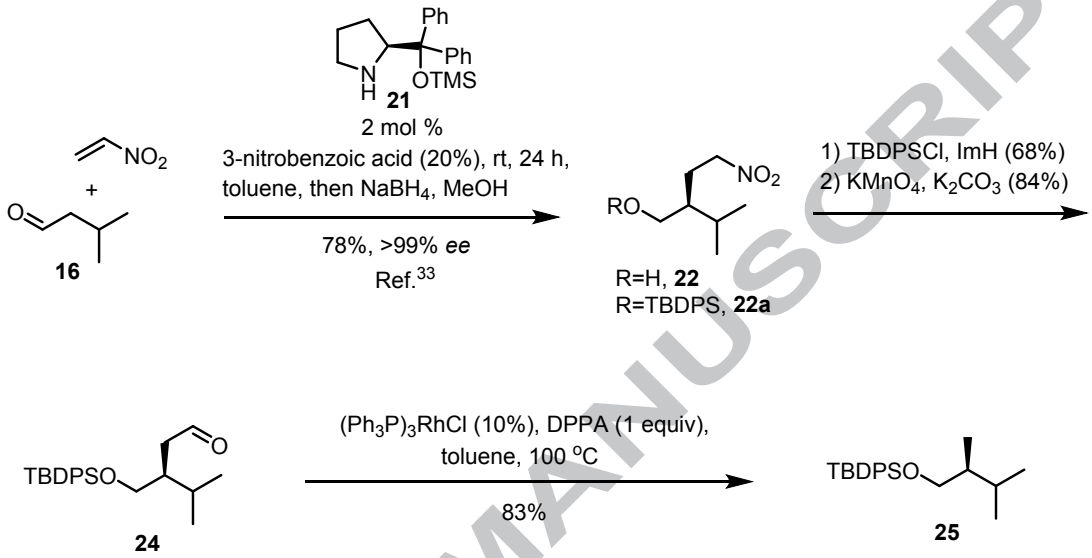
[b] Assigned by DEPT, COSY, HSQC, and HMBC experiments.

[c] *J* values (in Hz) in parentheses.

3 Results and Discussion

C23-C28 subunits **17-20**, **23** are small bulky molecules bearing a stereocenter and a functional group required for their further coupling with a steroidal core. Although the molecules are small, their synthesis is a laborious task associated with necessity of large quantity of chiral chemicals and volatility of the intermediates. Nitroalcohol **22** is a chiral compound easily accessible through the reported by Gellman organocatalytic Michael addition of isovaleraldehyde to nitroethylene [33] (Scheme 2). For its preparation, only 2% of easily available from natural L-proline catalyst **21** [37, 38] is necessary and we assumed that compound **22** might be a good starting point in synthesis of the target subunit if we develop an efficient way of the nitromethyl group removal. As far as this group can be easily transformed to an aldehyde or acid moiety, decarbonylation or decarboxylation reactions can be used to form the required hydrocarbon backbone. At the beginning, we tested decarbonylation strategy based on the rhodium-catalyzed reaction of aldehydes reported by O'Connor [39]. Taking into account a significant increase in volatility of the molecule after decarbonylation, the hydroxyl group in **22** was protected as a TBDPS ether. To transform the nitromethyl group into the aldehyde, the silylated nitroalcohol was reacted with potassium carbonate and potassium permanganate according to Steliou's protocol [40]. Attempts to prepare aldehyde **24** by either a sequence of the base-mediated nitronate formation followed by its acid-catalyzed hydrolysis [41] or by the reaction with sodium peroxocarbonate [42] were unsuccessful. The best result on decarbonylation of aldehyde **24** was achieved when the substrate was heated at 100^{o}C in toluene in the presence of 10% of Wilkinson's catalyst and 1 equiv of DPPA [39]. Delightfully, the yield of the reaction was higher than that in stoichiometric version of the reaction (entries 1-2). Changing the solvent to THF, which was originally used by O'Connor and coworkers [39], was detrimental for the reaction (entries 3-4). Decreasing of amount of the catalyst to 5% resulted in significant decrease in the yield (entry 5). Attempts of decarbonylation of **24** under palladium catalysis [43] were unsuccessful and resulted only in recovery of the starting material or formation of complex mixtures. Although overall yield of **25** was good enough, the

necessity of using the expensive rhodium catalyst encouraged us to continue our search for an alternative way of dehomologation of **22**. One more disadvantage of the developed approach was observed on the stage of desilylation of **25** by tetrabutylammonium fluoride (not shown). Separation of the formed volatile alcohol from TBDPSF was impossible in our hands.



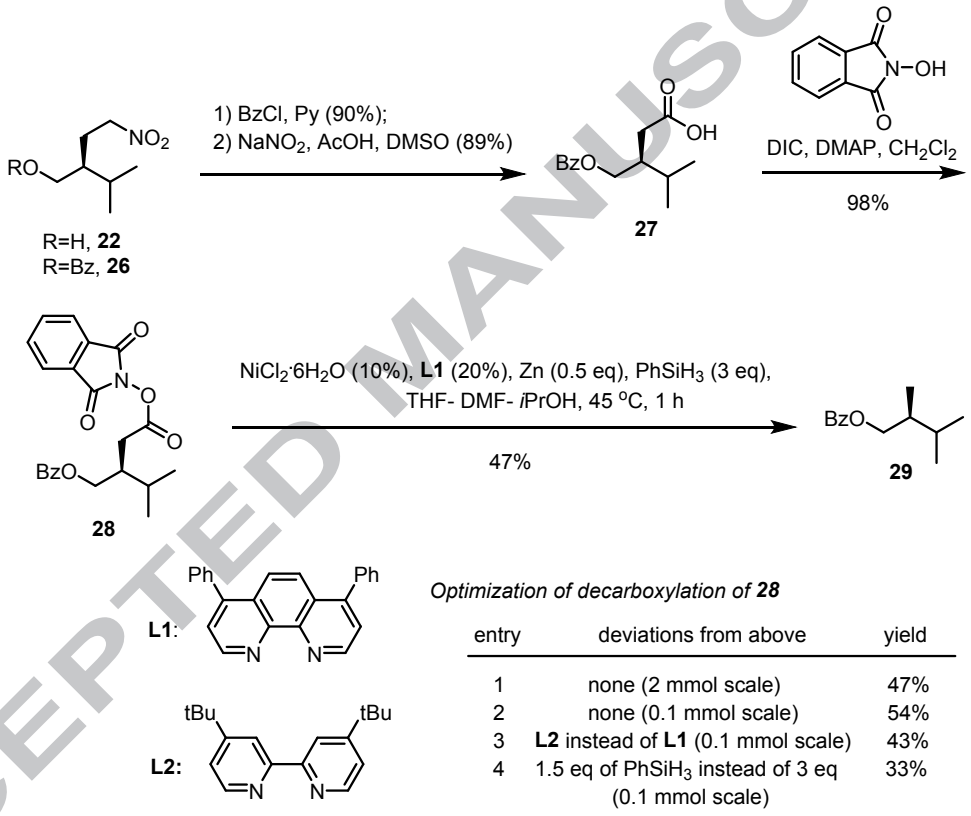
*Optimization of rhodium-catalyzed decarbonylation of **24***

entry	deviations from above	yield
1	none	83%
2	100% of $(Ph_3P)_3RhCl$, without DPPA	72%
3	THF instead of toluene, rt	0%
4	THF instead of toluene, 60 °C	0%
5	5% of $(Ph_3P)_3RhCl$	54%

Scheme 2. Synthesis of the ether **25**

Both of the disadvantages mentioned above were overcome when decarboxylation reaction was used as a key step instead of decarbonylation. Precious-metal catalysis is not necessary for hydrodecarboxylation, which can be performed under nickel catalysis [44] or in the presence of organic photoredox catalyst under irradiation by visible light [45]. Moreover, nitromethyl group can be transformed to acid moiety under acidic conditions [46] permitting protection of the hydroxyl group in **22** as an ester instead of silyl ether. At first, the hydroxyl group in nitroalcohol **22** was benzoylated and the carboxylic acid unit was formed by the reaction of the protected **26** with sodium nitrite and acetic acid (Scheme 3). Initially, we tried to decarboxylate unactivated acid **27** under photoredox catalysis [45] but only recovery of the starting material was observed. The desired transformation was successfully accomplished using the protocol recently reported by Baran [44]. Carboxylic acid **27** was transformed to

NHPI ester **28** that was engaged into the nickel-catalyzed decarboxylation. An acceptable 47% yield of **29** was achieved in the presence of 20% of bathophenanthroline (**L1**) as a ligand when the reaction was carried out on a 2 mmol scale (entry 1). At a scale lowered to 0.1 mmol, the yield was only a little higher (entry 2). In the presence of 4,4′-di-*tert*-butyl-2,2′-dipyridyl (**L2**) ligand, the reaction proceeded less efficiently (entry 3). Amount of phenylsilane had a significant effect on the yield of the reaction, which was greater in the presence of 3 eq of the source of hydrogen as compared to the experiment when only 1.5 eq were added (entries 2 and 4).



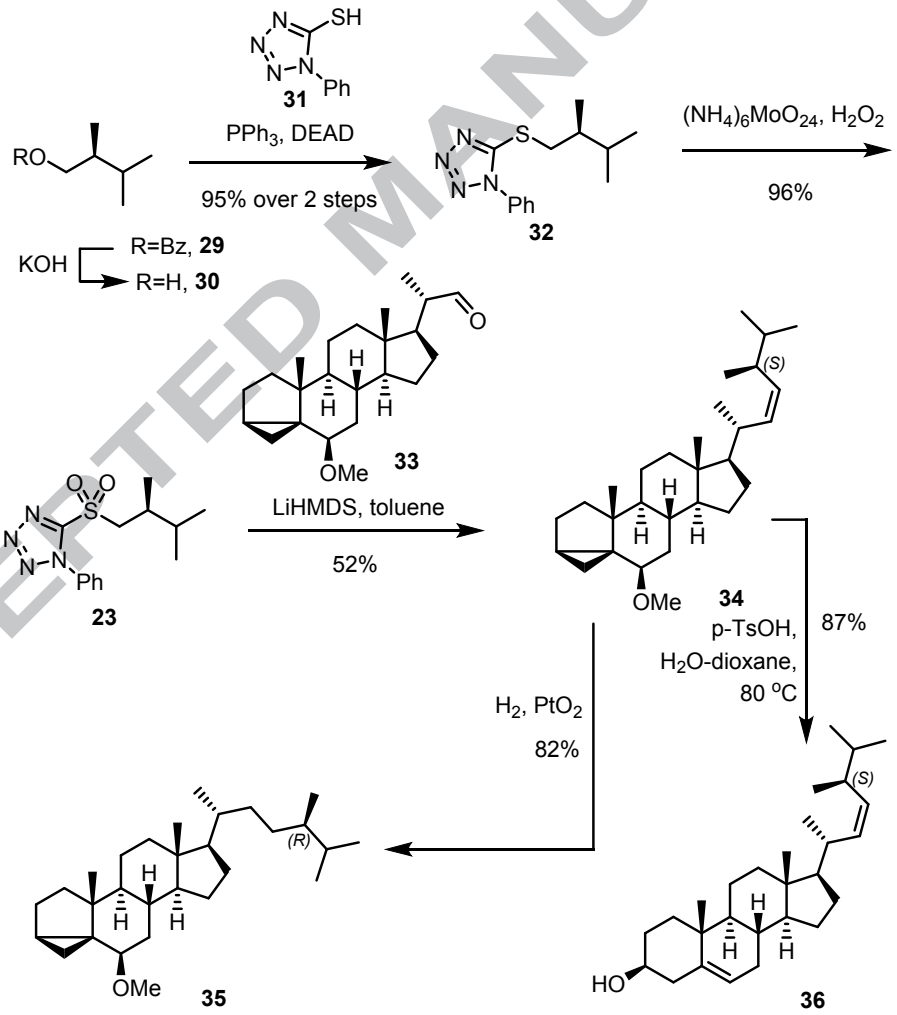
*Optimization of decarboxylation of **28***

entry	deviations from above	yield
1	none (2 mmol scale)	47%
2	none (0.1 mmol scale)	54%
3	**L2** instead of **L1** (0.1 mmol scale)	43%
4	1.5 eq of $PhSiH_3$ instead of 3 eq (0.1 mmol scale)	33%

Scheme 3. Ni-catalyzed decarboxylation of NHPI redox-active ester **28**

With benzoate **29** in hands, we easily synthesized the target C23-C28 subunit **23** bearing phenyltetrazolylsulfonyl moiety (Scheme 4). Saponification of **29** furnished the volatile alcohol **30**, which, without purification, was coupled with thiol **31** giving thioether **32** in a 95% yield over 2 steps. Finally, oxidation of **32** afforded the required sulfone **23** in a 96% yield, which was further successfully employed in construction of saturated and unsaturated campestane side chains. The Julia-Kocienski olefination [47, 48] of steroidal aldehyde **33** with lithiated sulfone **23** furnished an unusual for this reaction *Z*-isomer of steroid **34** (*Z*:*E* = 25:1). Configuration of the alkenyl unit was confirmed by 2D NOESY NMR experiment

(see SI). The obtained alkene was rearranged to (*Z*)-22-dehydrocampesterol (**36**), which is a rare and poorly studied component of biological membranes [49-54]. As far as campestane steroids bearing 22*E*-alkenyl fragment are demanded as synthetic intermediates and naturally occurring as well, we tried to alter the selectivity of the olefination. Typically, *E*-selectivity in the Julia-Kocienski reaction can be increased by changing the base from LiHMDS to KHMDS [ref]. However, under the modified conditions, we observed significant drop of the yield of **34** to 7% and only moderate selectivity of the reaction (*Z*:*E* =45:55). The saturated campestane side chain is presented in such steroids as campesterol (**1**) and swinhoeisterol A (**5**) and this unit can be easily formed by simple platinum-catalyzed hydrogenation of **34**, which proceeds smoothly giving steroid **35** in a 82% yield.



Scheme 4. Synthesis of **23** and its application in construction of the campestane side chain

Conclusion

In conclusion, a catalytic way to C23-C28 subunit of 24α-methyl steroids has been developed. The approach is based on dehomologation of (*S*)-2-isopropyl-4-nitrobutan-1-ol, which is easily available on

multigram scale *via* an asymmetric reaction catalyzed by only 2% of an organocatalyst. Removal of the extra carbon atom from this molecule was efficiently performed through a sequence of nitromethyl to carboxyl group transformation and nickel-catalyzed decarboxylation of the obtained acid after its activation. The synthesized C23-C28 fragment bearing phenyltetrazolylsulfonyl group is suitable for its coupling with a steroidal aldehyde by the Julia-Kocienski reaction and we have successfully constructed side chains presented in such steroids as campestane, swinhoeisterol A and (*Z*)-22-dehydrocampesterol.

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References

[1] H. Schaller, The role of sterols in plant growth and development, Prog. Lipid Res. 42(3) (2003) 163-175. https://doi.org/10.1016/S0163-7827(02)00047-4.

[2] L.J. Goad, G.G. Holz, D.H. Beach, Identification of (24*S*)-24-methylcholesta-5,22-dien-3β-ol as the major sterol of a marine cryptophyte and a marine prymnesiophyte, Phytochemistry 22(2) (1983) 475-476. https://doi.org/10.1016/0031-9422(83)83028-3.

[3] M.D. Grove, G.F. Spencer, W.K. Rohwedder, N. Mandava, J.F. Worley, J.D. Warthen, G.L. Steffens, J.L. Flippen-Anderson, J.C. Cook, Brassinolide, a plant growth-promoting steroid isolated from *Brassica napus* pollen, Nature 281(5728) (1979) 216-217. https://doi.org/10.1038/281216a0.

[4] V.A. Khripach, V.N. Zhabinskii, A. de Groot, Brassinosteroids. A New Class of Plant Hormones, Academic Press, San Diego, 1999.

[5] M.F. Feldlaufer, E.W. Herbert, J.A. Svoboda, M.J. Thompson, W.R. Lusby, Makisterone A: The major ecdysteroid from the pupa of the honey bee, Apis mellifera, Insect Biochemistry 15(5) (1985) 597-600. https://doi.org/10.1016/0020-1790(85)90120-9.

[6] J. Gong, P. Sun, N. Jiang, R. Riccio, G. Lauro, G. Bifulco, T.-J. Li, W.H. Gerwick, W. Zhang, New steroids with a rearranged skeleton as (h)P300 inhibitors from the sponge *Theonella swinhoei*, Org. Lett. 16(8) (2014) 2224-2227. https://doi.org/10.1021/ol5007345.

[7] J. Li, H. Tang, T. Kurtán, A. Mándi, C.-L. Zhuang, L. Su, G.-L. Zheng, W. Zhang, Swinhoeisterols from the South China Sea Sponge Theonella swinhoei, J. Nat. Prod. 81(7) (2018) 1645-1650. https://doi.org/10.1021/acs.jnatprod.8b00281.

[8] M. Anastasia, P. Allevi, P. Ciuffreda, A. Fiecchi, Stereoselective synthesis of crinosterol [(22*E*,24*S*)-ergosta-5,22-dien-3β-ol], J. Chem. Soc., Perkin Trans. 1 (10) (1983) 2365-2367. https://doi.org/10.1039/P19830002365.

[9] S. Takatsuto, N. Ikekawa, Synthesis of [26,28-$^2H_6$]crinosterol, a synthetic intermediate of [26,28-$^2H_6$]brassinolide and [26,28-$^2H_6$]castasterone, J. Chem. Soc., Perkin Trans. 1 (4) (1986) 591-593. https://doi.org/10.1039/P19860000591.

[10] V.A. Khripach, V.N. Zhabinskii, O.V. Konstantinova, N.B. Khripach, A.P. Antonchick, B. Schneider, [3,3]-Claisen rearrangements in 24α-methyl steroid synthesis: Application to campesterol, crinosterol, and Δ^{25}-crinosterol side chain construction, Steroids 67(7) (2002) 597-603. https://doi.org/10.1016/S0039-128X(02)00007-7.

[11] V.A. Khripach, V.N. Zhabinskii, Y.V. Ermolovich, O.V. Gulyakevich, Synthesis of [26-$^2H_3$]-campesterin and [26-$^2H_3$]-campestanol, deuterated analogs of biosynthetic precursors of 28C-brassinosteroids, Chem. Nat. Compd. 48(4) (2012) 606-609. https://doi.org/10.1007/s10600-012-0323-0.

[12] A.L. Hurski, V.N. Zhabinskii, V.A. Khripach, A new approach to the side chain formation of 24-alkyl-22-hydroxy steroids: application to the preparation of early brassinolide biosynthetic precursors, Steroids 77(7) (2012) 780-790. https://doi.org/10.1016/j.steroids.2012.03.010.

[13] V.A. Khripach, V.N. Zhabinskii, O.V. Konstantinova, A.P. Antonchick, B. Schneider, Synthesis of [26-$^2H_3$]brassinosteroids, Steroids 67(7) (2002) 587-595. https://doi.org/10.1016/S0039-128X(02)00004-1.

[14] V.A. Khripach, V.N. Zhabinskii, O.V. Konstantinova, N.B. Khripach, Ireland-Claisen rearrangement of steroidal Δ^{23}-22-alcohols: an application to $\Delta^{22,25}$-24-alkyl steroid synthesis, Tetrahedron Lett. 41(30) (2000) 5765-5767. https://doi.org/10.1016/S0040-4039(00)00900-X.

[15] V.A. Khripach, V.N. Zhabinskii, N.D. Pavlovskii, Synthesis of (22*R*,23*R*,24*S*)-24-methyl-5α-cholestane-3β,6α,22,23-tetraol, a biosynthetic precursor of brassinolide, Russ. J. Org. Chem. 37(11) (2001) 1570-1574. https://doi.org/10.1023/A:1013804119279.

[16] K. Mori, M. Sakakibara, Y. Ichikawa, H. Ueda, K. Okada, T. Umemura, G. Yabuta, S. Kuwahara, M. Kondo, M. Minobe, A. Sogabe, Synthesis of (22*S*,23*S*)-homobrassinolide and brassinolide from stigmasterol, Tetrahedron 38(14) (1982) 2099-2109. https://doi.org/10.1016/0040-4020(82)85157-0.

[17] T. Schmittberger, D. Uguen, A formal synthesis of brassinolide, Tetrahedron Lett. 38(16) (1997) 2837-2840. https://doi.org/10.1016/S0040-4039(97)00474-7.

[18] V.A. Khripach, V.N. Zhabinskii, A.P. Antonchick, O.V. Konstantinova, B. Schneider, Synthesis of hexadeuterated 23-dehydroxybrassinosteroids, Steroids 67(13-14) (2002) 1101-1108. https://doi.org/10.1016/S0039-128X(02)00071-5.

[19] V.A. Khripach, V.N. Zhabinskii, K.V. Parkhimovich, O.V. Gulyakevich, Synthesis of brassinolide and its biosynthetic precursors using methyl-3-hydroxy-2-methylpropionate, Russ. J. Bioorg. Chem. 35(2) (2009) 240-249. https://doi.org/10.1134/S1068162009020137.

[20] A.P. Antonchick, B. Schneider, V.N. Zhabinskii, V.A. Khripach, Synthesis of [26,27-$^2H_6$]brassinosteroids from 23,24-bisnorcholenic acid methyl ester, Steroids 69(10) (2004) 617-628. https://doi.org/10.1016/j.steroids.2004.05.014.

[21] N.M. O'Connell, Y.C. O'Callaghan, N.M. O'Brien, A.R. Maguire, F.O. McCarthy, Synthetic routes to campesterol and dihydrobrassicasterol: a first reported synthesis of the key phytosterol dihydrobrassicasterol, Tetrahedron 68 (2012) 4995-5004. https://doi.org/10.1016/j.tet.2012.04.060.

[22] P. Ferraboschi, E. Santaniel, A convenient synthesis of (*S*)-2-methyl and (2*S*)-2,3-dimethyl butyl phenylsulfones from (*S*)-(-)-3-methyl-γ-butyrolactone, Synth. Commun. 14(13) (1984) 1199-1204. https://doi.org/10.1080/00397918408076800.

[23] R. Kiesgen de Richter, M. Bonato, M. Follet, J.M. Kamenka, The (+)- and (-)-[2-(1,3-dithianyl)]myrtanylborane. Solid and stable monoalkylboranes for asymmetric hydroboration, J. Org. Chem. 55(9) (1990) 2855-2860. https://doi.org/10.1021/jo00296a054.

[24] M. Sato, N. Miyaura, A. Suzuki, Rhodium(I)-catalyzed asymmetric hydroboration of alkenes with 1,3,2-benzodioxaborole, Tetrahedron Lett. 31(2) (1990) 231-234. https://doi.org/10.1016/S0040-4039(00)94379-X.

[25] A.Z. Gonzalez, J.G. Roman, E. Gonzalez, J. Martinez, J.R. Medina, K. Matos, J.A. Soderquist, 9-Borabicyclo[3.3.2]decanes and the asymmetric hydroboration of 1,1-disubstituted alkenes, J. Am. Chem. Soc. 130(29) (2008) 9218-9219. https://doi.org/10.1021/ja803119p.

[26] H.C. Brown, R.G. Naik, R.K. Bakshi, C. Pyun, B. Singaram, Synthetic utility of boronic esters of essentially 100% optical purity. Synthesis of homologated boronic acids and esters of very high enantiomeric purities, J. Org. Chem. 50(26) (1985) 5586-5592. https://doi.org/10.1021/jo00350a031.

[27] T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, H. Takaya, Highly efficient enantioselective synthesis of optically active carboxylic acids by $Ru(OCOCH_3)_2$[(*S*)-H_8-BINAP], J. Org. Chem. 61(16) (1996) 5510-5516. https://doi.org/10.1021/jo960426p.

[28] G. Filippini, M. Silvi, P. Melchiorre, Enantioselective formal α-methylation and α-benzylation of aldehydes by means of photo-organocatalysis, Angew. Chem., Int. Ed. 56(16) (2017) 4447-4451. https://doi.org/10.1002/anie.201612045.

[29] L.F. Tietze, C. Raith, C.C. Brazel, S. Hölsken, J. Magull, Enantioselective synthesis of 2-substituted alcohols using (+)-(1*S*,2*S*)-pseudoephedrine as chiral auxiliary, Synthesis 2008(02) (2008) 229-236. https://doi.org/10.1055/s-2008-1000851.

[30] K.-C. Cheng, B. Luu, G. Ourisson, J.P. Beck, Chemistry and biochemistry of Chinese drugs. Part IV. Stereoselective partial synthesis and cytotoxicity of 7- and 22-

hydroxylated derivatives of 24-methylcholesterols, J. Chem. Res., Synop. (3) (1979) 84-85.

[31] J. Hang, P. Dussault, A concise synthesis of β-sitosterol and other phytosterols, Steroids 75(12) (2010) 879-883. https://doi.org/10.1016/j.steroids.2010.05.016.

[32] A. Hurski, V. Zhabinskii, V. Khripach, A short convergent synthesis of the side chains of brassinolide, cathasterone, and cryptolide, Tetrahedron Lett. 54(6) (2013) 584-586. https://doi.org/10.1016/j.tetlet.2012.11.094.

[33] Y. Chi, L. Guo, N.A. Kopf, S.H. Gellman, Enantioselective organocatalytic Michael addition of aldehydes to nitroethylene: efficient access to γ^2-amino acids, J. Am. Chem. Soc. 130(17) (2008) 5608-5609. https://doi.org/10.1021/ja800345r.

[34] W.L.E. Armarego, Purification of Laboratory Chemicals, 8th ed., Butterworth-Heinemann, Amsterdam, 2017.

[35] J.A. Steele, E. Mosettig, The solvolysis of stigmasteryl tosylate, J. Org. Chem. 28(2) (1963) 571-572. https://doi.org/10.1021/jo01037a505.

[36] J.J. Pappas, W.P. Keaveney, E. Gancher, M. Berger, A new and convenient method for converting olefins to aldehydes, Tetrahedron Lett. 7(36) (1966) 4273-4278. https://doi.org/10.1016/S0040-4039(00)76049-7.

[37] K.L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K.A. Jørgensen, The diarylprolinol silyl ether system: a general organocatalyst, Acc. Chem. Res. 45(2) (2012) 248-264. https://doi.org/10.1021/ar200149w.

[38] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, Diphenylprolinol silyl ethers as efficient organocatalysts for the asymmetric Michael reaction of aldehydes and nitroalkenes, Angew. Chem., Int. Ed. 44(27) (2005) 4212-4215. https://doi.org/doi:10.1002/anie.200500599.

[39] J.M. O'Connor, J. Ma, Metal-catalyzed decarbonylation of primary aldehydes at room temperature, J. Org. Chem. 57(19) (1992) 5075-5077. https://doi.org/10.1021/jo00045a015.

[40] K. Steliou, M.A. Poupart, Synthesis of aldehydes and ketones from nitro paraffins, J. Org. Chem. 50(24) (1985) 4971-4973. https://doi.org/10.1021/jo00224a067.

[41] H. Chikashita, Y. Morita, K. Itoh, Transformation of aromatic nitroalkanes into carbonyl compounds by the improved Nef reaction, Synth. Commun. 17(6) (1987) 677-683. https://doi.org/10.1080/00397918708075741.

[42] C. Narayana, N.K. Reddy, G.W. Kabalka, Sodium percarbonate: a mild reagent for conversion of tosylhydrazones and nitroalkanes to carbonyl compounds, Synth. Commun. 22(17) (1992) 2587-2592. https://doi.org/10.1080/00397919208021655.

[43] A. Modak, A. Deb, T. Patra, S. Rana, S. Maity, D. Maiti, A general and efficient aldehyde decarbonylation reaction by using a palladium catalyst, Chemical Communications 48(35) (2012) 4253-4255. https://doi.org/10.1039/C2CC31144E.

[44] T. Qin, L.R. Malins, J.T. Edwards, R.R. Merchant, A.J. Novak, J.Z. Zhong, R.B. Mills, M. Yan, C. Yuan, M.D. Eastgate, P.S. Baran, Nickel-catalyzed Barton decarboxylation and Giese reactions: a practical take on classic transforms, Angew. Chem., Int. Ed. 56(1) (2017) 260-265. https://doi.org/10.1002/anie.201609662.

[45] J.D. Griffin, M.A. Zeller, D.A. Nicewicz, Hydrodecarboxylation of carboxylic and malonic acid derivatives via organic photoredox catalysis: substrate scope and mechanistic insight, J. Am. Chem. Soc. 137(35) (2015) 11340-11348. https://doi.org/10.1021/jacs.5b07770.

[46] C. Matt, A. Wagner, C. Mioskowski, Novel transformation of primary nitroalkanes and primary alkyl bromides to the corresponding carboxylic acids, J. Org. Chem. 62(2) (1997) 234-235. https://doi.org/10.1021/jo962110n.

[47] P.R. Blakemore, The modified Julia olefination: alkene synthesis via the condensation of metallated heteroarylalkylsulfones with carbonyl compounds, J. Chem. Soc., Perkin Trans. 1 (23) (2002) 2563-2585. https://doi.org/10.1039/B208078H.

[48] P.R. Blakemore, W.J. Cole, P.J. Kocieński, A. Morley, A stereoselective synthesis of *trans*-1,2-disubstituted alkenes based on the condensation of aldehydes with metallated 1-phenyl-1*H*-tetrazol-5-yl sulfones, Synlett 29(1) (1998) 26-28. https://doi.org/10.1055/s-1998-1570.

[49] S. De Rosa, A. Milone, S. Popov, S. Andreev, Sterol composition of the Black Sea Hydrozoan, *Obelia longissima* (Pallas 1766), Comp. Biochem. Physiol. Part B: Biochem. Mol. Biol. 123(2) (1999) 229-233. https://doi.org/10.1016/S0305-0491(99)00065-6.

[50] K. Slantchev, K. Stefanov, K. Seizova, S. Popov, S. Andreev, Chemical Composition of the Lipophylic Extract from the Tunicate *Botryllus schlosseri*, Zeitschrift für Naturforschung C 55(9-10) (2000) 794-798. https://doi.org/10.1515/znc-2000-9-1020.

[51] K. Slantchev, F. Yalçın, T. Ersöz, J. Nechev, İ. Çalış, K. Stefanov, S. Popov, Composition of Lipophylic Extracts from Two Tunicates, *Styela* sp. and *Phallusia* sp. from the Eastern Mediterranean, Zeitschrift für Naturforschung C 57(5-6) (2002) 534-540. https://doi.org/10.1515/znc-2002-5-623.

[52] S. De Rosa, Z. Kamenarska, V. Bankova, K. Stefanov, S. Dimitrova-Konaklieva, H. Najdenski, I. Tzevtkova, S. Popov, Chemical composition and biological activities of the Black Sea algae *Polysiphonia denudata* (Dillw.) Kutz. and *Polysiphonia denudata f.*

fragilis (Sperk) Woronich, Zeitschrift für Naturforschung C 56(11-12) (2001) 1008-1014. https://doi.org/10.1515/znc-2001-11-1218.

[53] T. Akihisa, T. Tamura, T. Matsumoto, W.C.M.C. Kokke, P. Ghosh, S. Thakur, (22*Z*,24*S*)-Stigmasta-5,22,25-trien-3β-ol and other novel sterols from *Clerodendrum scandens*: first report of the isolation of a cis-Δ^{22}-unsaturated sterol from a higher plant, J. Chem. Soc., Perkin Trans. 1 (8) (1990) 2213-2218. https://doi.org/10.1039/P19900002213.

[54] S.-I. Teshima, A. Kanazawa, T. Ando, A new C28-sterol: Isolation of 22-cis-24-Ξ-methylcholesta-5,22-dien-3β-ol, Comparative Biochemistry and Physiology Part B: Comparative Biochemistry 47(2) (1974) 507-514. https://doi.org/https://doi.org/10.1016/0305-0491(74)90081-9.

Legends

Fig. 1. Structures of some natural steroids with a campestane side chain

Scheme 1. Approaches to the synthesis of campestane side chains **9,10** and C23-C28 fragments **17-20**, **23**

Scheme 2. Synthesis of the ether **25**

Scheme 3. Ni-catalyzed decarboxylation of NHPI redox-active ester **28**

Scheme 4. Synthesis of **23** and its application in construction of the campestane side chain

Table 1 – ^{1}H and ^{13}C NMR spectroscopic data for compounds **32** and **33**[a,b,c]

Contacts

Viktoryia S. Yakimchyk, yakimchik.victoria@gmail.com, https://orcid.org/0000-0001-5657-5346

Volha V. Kazlova, okozlova.94@gmail.com, https://orcid.org/0000-0003-2039-9509

Alaksiej L. Hurski, ahurski@iboch.by, https://orcid.org/0000-0002-8599-2621

Rimma G. Savchenko, rimasavchenko@mail.ru, https://orcid.org/0000-0001-9145-2253

Svetlana A. Kostyleva, skostyleva_89@mail.ru, https://orcid.org/0000-0002-9524-9460

Vladimir Zhabinskii, vz@iboch.by, https://orcid.org/0000-0001-8591-2794

Vladimir Khripach, khripach@iboch.by, https://orcid.org/0000-0002-3850-9860

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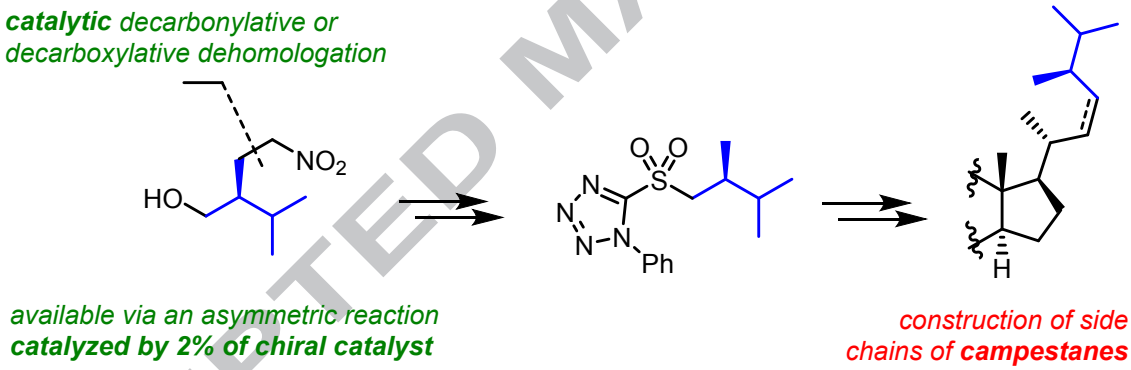

- A new catalytic way to C23-C28 fragment of campestanes is reported
- The synthesis is based on organocatalytic formation of the stereocenter followed by dehomologation of the obtained synthetic intermediate
- The synthesized subunit can be attached to a steroidal core by Julia-Kocienski olefination