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Published in:
Journal of Organic Chemistry

DOI:
10.1021/jo4005298

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Synthesis and analysis of the all-(S) side chain of phosphomycoketides: a test of NMR predictions for saturated oligoisoprenoid stereoisomers

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The large scale preparation of isoprenoid building block 12 was crucial because it was used twice in the synthesis (Scheme S1). Dienone 9 was prepared by double oxidation of cyclooctanone 8 with IBX, which was then subjected to a copper-catalyzed asymmetric 1,4-addition employing Feringa’s ligand L1, to provide 10 in 80% yield and 98% ee. Repetition of the asymmetric 1,4-addition, this time with the enantiomer of the copper catalyst, and subsequent trapping of the enolate with TMSCl, resulted in silylenol ether 11. Oxidative ring-opening with ozone followed by esterification with methanol gave isoprenoid 12 in 60% yield over 4 steps as a single diastereomer and enantiomer (>99% ee).

Alcohol 12 served as a precursor to both aldehyde 18, obtained by a TPAP mediated oxidation (96% yield), and sulfone 17. The sulfone was synthesized via TBDPS protection of the alcohol 12, reduction of the ester and subsequent Mitsunobu reaction of 14 with 1-phenyl-1H-tetrazole-5-thiol 15. The resulting thioether 16 was then oxidized to the corresponding sulfone 17, completing the four step sulfone synthesis procedure in 72% overall yield.

Sulfone 17 and aldehyde 18 were connected in a Julia-Kocienski reaction,¹² which smoothly provided alkene 19 in a 2:1 E:Z isomer mixture in 83% yield. The synthesis of 4 was completed by a straightforward three-step sequence of ester reduction, tosylation, and alkylation to give key intermediate 4 in good yield. Subsequent NMR studies of the final product 3c (see below) led us to question the stereochemical integrity of 4. To assess this, we carefully saturated a small sample of the (E)/(Z) isomer mixture of 4 to give 7. This sample was isomerically pure (see below) so by implication all the reactions leading to 4 occurred with high stereoselectivity and the so-formed stereocenters were retained with fidelity.
The synthesis of the final needed fragment 5 and the completion of the synthesis of 3c are shown in Scheme S2. Construction of sulfone 5 started with readily available aldehyde 21, which was employed in a Wittig reaction to give α,β-unsaturated thioester 22. Introduction of the fifth stereocenter was achieved by copper/Josiphos (L2) catalyzed asymmetric 1,4-addition in 94% yield and 89% ee. Reduction of thioester 23 with LiAlH4 proceeded in 95% yield, and then the resulting alcohol was converted into the sulfone 5 by the same steps as in Scheme S1.

To finish the synthesis, TBDPS ether 4 was desilylated (95% yield) and the resulting alcohol 26 was oxidized by TPAP (97% yield) to afford aldehyde 27. The Julia-Kocienski reaction involved deprotonation of sulfone 5 with LiHMDS at –78 °C, subsequent addition of aldehyde...
27 and warming to rt. Workup gave 6, in 81% yield, presumably as an E/Z mixture at both alkenes (the (6E,14E)-isomer is the major product, as shown). Careful hydrogenation with palladium on carbon provided MPM side chain sample 3c in 92% yield.

Scheme S2. Synthesis of the final fragment 5 and completion of the synthesis of MPM side chain 3c.

(a) Synthesis of sulfone 5

(b) Completion of the synthesis of 3c

Conditions: a) Ph₃PC(OSEt (1.1 equiv), CHCl₃, reflux, 3 h; b) DMAP (25 mol%); CHCl₃, rt; c) CuBr•SMe₂ (5 mol%); [(R,S)-Josiphos L₂ (6 mol%); MeMgBr (1.3 equiv), TBME, –78 °C; d) LiAlH₄ (2.5 equiv), THF, –78 °C, 1 h; e) 24 (2 equiv), Ph₃P (1.5 equiv), DIAD (1.8 equiv); THF, 0 °C to rt, 1 h; f) mCPBA (5 equiv), CH₂Cl₂, 0 °C to rt; g) TBAF (3 equiv), THF, rt, 3 h; h) TPAP (2 mol%), NMO (1.2 equiv), 4 Å mol sieves, CH₂Cl₂, rt, 2 h; i) LiHMDS (1 equiv), 4 (1 equiv), then 27 (1.15 equiv); THF, –78 °C to rt; j) Pd/C (10 mol%), H₂ (1 bar), CH₂Cl₂/MeOH (2:1), rt.
**General Information on NMR Experiments:**

The NMR spectra were recorded on a 700 MHz spectrometer using deuterated chloroform spiked with 1% trimethylsilane (TMS), unless otherwise indicated. The signals are given as in parts per million (δ, ppm) and were determined relative to the proton and carbon resonance of TMS at 0 ppm as the internal standard. For the resolution-enhanced spectra of 3c and 7, data were collected and processed as described in Traficante, D. D.; Nemeth, G. A. *J. Magn. Reson.* **1987**, *71*, 237-245.

Copies of predicted ¹H and ¹³C NMR spectra of all stereoisomers of both 3b and 3c (48 spectra total) are found in the Supporting Information associated with Yeh, E. A.; Kumli, E.; Damodaran, K.; Curran, D. P. *J. Am. Chem. Soc.* **2013**, *135*, 1577-1584.
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MPM Sidechain Spectra

3c

HO

C₅H₁₁

ppm

8  7  6  5  4  3  2  1  0
1H NMR &
Selective TOCSY

1st CH₃

2nd CH₃
$^1$H-$^{13}$C 2D correlation (major isomer peaks)
$^{1}H-^{13}C$ 2D correlation
(major and minor isomer peaks)
Minnaard Cmpd 18, 1H, 700, 2/14/12

Owen Budavich, Curran Group, University of Pittsburgh

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MPM Sidechain Spectra

TBDPSO
Minnaard Cmpd 18, 1H, 700, 2/14/12

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Minnaard Cmpd 18, 1H, 700, 2/14/12

MPM Sidechain Spectra

TBDPSO
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Owen Budavich, Curran Group, University of Pittsburgh
Minnaard Cmpd 18, 1H, 700, 2/14/12

TBDPSO

MPM Sidechain Spectra
OB-NB-094-078, 700 MHz, CDCl3

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MPM Sidechain Spectra

TBDPSO
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MPM Sidechain Spectra

S16
High Resolution 1H NMR spectrum

TBDPSO

1  2  3  4

5th CH₃

5th CH₃
Selective TOCSY NMR

Selective irradiation of $\text{CH}_2\text{-O-Si}$

1st CH$_3$
Selective TOCSY NMR

Selective irradiation of 1st CH₃

TBDPSO

1st CH₃

2nd CH₃

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MPM Sidechain Spectra
2D-TOCSY NMR

4th and 5th CH₃ are connected to the same bunch of CH₂

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MPM Sidechain Spectra

S20
2D-TOCSY NMR

2\textsuperscript{nd} and 3\textsuperscript{rd} \text{CH}_3 are connected to the same bunch of \text{CH}_2

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MPM Sidechain Spectra
$^{13}$C NMR Assignments

$^{13}$C-$^1$H 2D NMR Correlation Spectrum

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MPM Sidechain Spectra
$^{13}$C NMR Assignments

$^{13}$C- $^1$H 2D NMR Correlation Spectrum

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MPM Sidechain Spectra

TBDPSO