Gram-scale carbasugar synthesis via intramolecular seleno-Michael/aldol reaction†

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Carbasugars represent an important category of natural products possessing a broad spectrum of biological activities. Lots of effort has been done to develop gram scale synthesis. We are presenting a new approach to gram scale synthesis of the carbasugar skeleton via intramolecular seleno-Michael/aldol reaction. The proposed strategy gave gram amounts of 6-hydroxy shikimic ester in a tandem process in 36% overall yield starting from D-lyxose. We have attempted to demonstrate the synthetic utility of 6-hydroxyshikimic acid derivatives by covering the important synthetic modifications and related applications, namely synthesis of protected (−)-gabosine E, (−)-MK7606, (−)-valienamine and finally unprotected methyl (−)-shikimate.

Introduction

Carbasugars are analogues of sugars that have attracted the interest of medicinal chemists due to their potential application as active pharmaceutical ingredients. These compounds are structurally related to carbohydrates where the ring oxygen is replaced with a methylene group.1,2 Carbasugar fragments have been found in various natural products.3,4 The structural similarity of carbasugar fragments to conventional monosaccharides suggests that they are likely to bind and inhibit the same protein targets. The advantage of carbasugar containing compounds is the lack of a glycosidic linkage resulting in the increased stability toward enzymatic degradation.5,6 For example, synthetic nucleotide analogues containing thiosugar or carbasugars have been reported to be glycosyltransferase inhibitors.7–9 The mechanism of glycosidase inhibition has been studied and several carba-analogues, such as Sergliflozin-A10 or SL0101,11 have been introduced (Fig. 1). Growing interest of carbasugar use is limited due to their low availability from natural sources.

General strategies to obtain carbapyranoles can be broadly classified into two groups: (i) synthetic methods that employ non-carbohydrates as starting materials and (ii) protocols that utilize carbohydrates as precursors. Multi gram synthesis of carbasugar fragments is still challenging and extremely important.

Carbohydrates, especially monosaccharides, are excellent starting material for total synthesis of various natural and valuable synthetic compounds. Their availability is usually very high, prices are low and chemistry of carbohydrates is well known. An application of monosaccharides to carbohydrate mimetic synthesis seems to be a natural choice.12 General synthesis of carbasugars moieties is employing Grubbs cross metathesis reaction,13–16 aldol-type cyclization,17,18 Corey–Fuchs reaction19 and others.20 Total synthesis of gabosines has been recently reviewed by Mac and co-workers.21

Our proposal of shikimic-type esters synthesis and their reduced analogues is based on modification of 6-hydroxyshikimic ester11,22 obtained via intramolecular seleno-Michael/aldol reaction from D-lyxose (Scheme 1).

Results and discussion

First, we prepared oxo-α,β-unsaturated ester (8) according to the literature method in multi-gram scale.23 Mixture of 2,3,4-tri-O-benzyl-D-lyxopyranoses (6) have been refluxed with excess of ylide over 12 h yielding mixture of E/Z isomers of 7. Alcohol 7 has been oxidized to corresponding aldehyde 8 using Swern oxidation in 78% yield. Compound 8 has been subjected to intramolecular seleno-Michael/aldol reaction with consecutive oxidation-elimination process to afford a mixture of 6-hydroxyshikimic esters (5) in 56% yield for 7 h (Scheme 2).24

After short optimization, multistep tandem reaction gave the carbocyclic products (6S)-5 and (6R)-5 in 76% yield over 3 steps.
as an 1 : 0.33 mixture of axial and equatorial alcohol (Table 1). The 6S/R-isomers of 5 have been separated easily by column chromatography (Experimental section). Having established the optimized conditions for the cyclic core synthesis, further functionalization has been achieved.

### Synthesis of protected (−)-valienamine

The 6S-hydroxysikimic ester (6S)-5 has been transformed to non-natural valienamine derivative (11) with known protocol in 27% yield over 3 steps. Exposure of 10 to chlorosulfonyl isocyanate in DCM afforded the desired product (11) in 51% yield. Minor product has been assigned by NMR analysis as C3-epimer of (−)-valienamine (12) (Scheme 3).

### Synthesis of protected (−)-MK7607

Syn-isomer of compound 5 was transformed to partially protect unnatural (−)-MK7607. Simple reduction with DIBAL-H gave compound (6R)-9 in 33% yield which is surprising to the result obtained for 6S-isomer (65%) at the same conditions (Scheme 4).

### Synthesis of protected (−)-gabosine E

Starting from diastereomeric mixture of 5, ester fragment has been reduced in the presence of DIBAL-H to give diol 9 in 48% yield. Selective protection of primary hydroxyl group gave mixture of isomers 13 in 64% yield. Oxidation with Dess–Martin reagent in DCM to unsaturated ketone (14) and consecutive silyl ether deprotection gave 2,3,4-tri-O-benzylated (−)-gabosine E (15) in 84% yield in two steps (Scheme 5).

### Synthesis of methyl (−)-shikimate

(−)-Shikimic acid is an important metabolite in plants and microorganisms. This compound can be isolated from the Japanese star anise or synthetized starting from chiral and achiral substrates. Recently, Candeias et al.,25 summarized

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**Table 1** Scale optimization

| Entry | Scale | Conditions | Yield | Anti/syn |
|-------|-------|------------|-------|----------|
| 1     | 174 mg (0.35 mmol) | −20 °C (6 h) | 56% | 1 0.32 |
| 2     | 1080 mg (2.21 mmol) | −78 °C (30 min) | 76% | 1 0.32 |
| 3     | 5600 mg (11.45 mmol) | −78 °C (30 min) | 76% | 1 0.33 |

*Reaction conditions: THF, 1.2 equiv. n-BuSeLi to RT (30 min), 10 equiv. H₂O₂, 5 equiv. py, 50 °C (1 h).*

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**Scheme 2** Synthesis of key intermediate.

**Scheme 3** Synthesis of protected (−)-valienamine.

**Scheme 4** Synthesis of unnatural (−)-MK7607.

**Scheme 5** Synthesis of (−)-gabosine E derivative.
known methods of (−)-shikimic acid synthesis. Starting from
diastereomeric mixture of alcohols 5 several deoxygenation
methods have been tested (Table 2).

Finally, alcohol 5 was converted to mesylate 16. Unfortunately,
all of our attempts to displace the mesylate group with
hydride reagents resulted only in the 1,4-displacement. We
decided to change mesylate group to iodide (17) and we
found that halogenated compound (17) is unstable in the
presence of light. In the end, reduction of iodide crude
mixture carried out in the dark gave ethyl (−)-tri-O-benzyl-
shikimate (18) in 2 h in 73% yield over 3 steps. Ethyl ester
has been removed under basic conditions to give (−)-3,4,5-
tri-O-benzylshikimic acid in quantitative yield. Exposure of
19 to BCl₃ gave methyl (−)-shikimate (20) in 67% yield
(Scheme 6).

Table 2  Deoxygenation of 6-hydroxyshikimic acid

| Entry | Conditions | Yield |
|-------|------------|-------|
| 1     | Et₂SiH, BF₃, Et₂O, DCM, rt, 1 h | nr    |
| 2     | Et₂O, SiH, TFA, DCM, rt, up to 24 h | nr    |
| 3     | Tf₂, DCM – 40 °C, 30 min, 0 °C, 30 min then NaBH₄, EtOH | nr    |
| 4     | NaH, Im, 0 °C, 30 min, THF then CS₂, 30 min, rt, then MeI, 30 min, rt, 50 °C, 1 h | nr² |

² Xanthate not formed.

Scheme 6 Synthesis of methyl (−)-shikimate.

derivative enable access to selective modification of hydroxyl
groups. Deoxygenation of 6-hydroxyshikimic ester gave methyl
(−)-shikimate in 49% yield total.

Experimental

General experimental procedures

All starting materials and reagents were purchased from
commercial sources and used without purification. Reactions
were controlled using TLC on silica [alu-plates (0.2 mm)]. Plates
were visualized with UV light (254 nm) and by treatment with:
aqueous cerium(IV) sulfate solution with molybdic and sulfuric
acid followed by heating. All organic solutions were dried over
anhydrous magnesium sulfate. Reaction products were purified
by column chromatography using silica gel 60 (240–400 mesh).
Optical rotations were measured at room temperature with a
digital polarimeter. CDCl₃, D₂O, CD₃OD were used as NMR
solvents. ¹H spectra were recorded with 600 and 300 MHz, and
referenced relative to: CDCl₃ – solvent residual peak (δ = 7.26
ppm); D₂O – solvent residual peak (δ = 4.79 ppm); CD₃OD – solvent residual peak (δ = 3.31 ppm). Data are reported as
follows: chemical shift in parts per million (ppm), multiplicity (s
= singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd
= doublet of doublet of doublets, m = multiplet), coupling constants (in hertz) and integration. ¹³C NMR spectra were measured at 150
and 75 MHz with complete proton decoupling. Chemical shifts
were reported in ppm from the residual solvent as an internal
standard: CDCl₃ (δ = 77.16 ppm); CD₃OD (δ = 49.00 ppm).

High-resolution mass spectra were acquired using ESI-TOF
method.

2,3,4-Tri-O-benzyl-D-lyxopyranose (6)

To methanolic solution of 1% HCl (50 mL) (prepared by dis-
solving 1 mL SOCl₂ in anhydrous methanol) D-lyxose (5.0 g, 33.3
mmol) was added in one portion and resulting mixture was
refluxed for 5 h under argon (reaction was monitored by TLC
CH₂Cl₂/MeOH 2 : 1). The reaction mixture was allowed to cool
to room temperature, neutralized by addition of solid NaHCO₃
and brine (50 mL), then dried over anhydrous MgSO₄ and
concentrated under reduced pressure. The residue was
washed in EtOH (40 mL) and concentrated to the half of
the original volume, toluene (25 mL) was added and the mixture
was concentrated to dryness. The residue crude mixture oil was
used without further purification in the next step. The viscous
oil from the previous step was dissolved in anhydrous DMF (50
mL) and anhydrous THF (50 mL) and in 5 portion was added to
60% NaH suspension in mineral oil (6.8 g, 170 mmol) cooled to
0 °C. After hydrogen evolution was complete the mixture was
treated with BnBr (14.8 mL, 122 mmol) and stirred for 30 min in
0 °C and then 12 h in room temperature. The reaction mixture
was carefully quenched with cold, 10% aqueous solution of
NH₄Cl (30 mL) followed by addition of water (75 mL). The
aqueous layer was extracted with EtOAc (3 × 50 mL) and
combined organic layers were washed with water (2 × 60 mL)
and brine (50 mL), then dried over anhydrous MgSO₄ and
concentrated under reduced pressure. Crude mixture of D-

Conclusions

In summary, we have developed simple methods that provide
a rapid entry into the synthesis of a series of shikimate ester and
shikimate analogues, including (−)-gabosine E and
(−)-MK7606. Our synthesis of 6-hydroxy shikimates from D-lyx-
ose has been efficiently achieved in six steps with a 35% overall
yield. The strategies described take place through short, high-
yield reaction sequences. Partial protection of D-lyxose

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Ethyl (4R,5R,6R)-4,5,6-tri-O-benzyl-7-hydroxyhept-2-enoate (7)

To a solution of 6 (10.0 g, 23.8 mmol) in anhydrous benzene (200 mL), ethyl (triphenylphosphoranylidene)acetate (16.5 g, 47.6 mmol) was added in one portion and mixture was heated to reflux for 8 h. After that time next portion of ethyl (tribenzyloxyiminofunctional)acetate (8.3 g, 23.8 mmol) was added and heating to reflux was continued for next 4 h. Reaction mixture was cooled to room temperature and benzene was evaporated under reduced pressure. Most of triphenylphosphine oxide was precipitated from the mixture of Et₂O/Hex 7:3 and filtered by suction. Solvent was removed under reduced pressure and crude product was purified by column chromatography (Hex/EtOAc 3:1 to 7:3) to afford product as a colorless syrup (8.95 g, 18.2 mmol, 77%, Z/E = 1:0.6). 1H NMR (600 MHz, CDCl₃) δ 7.36–7.26 (m, 24H), 7.06 (dd, J = 15.9, 6.6 Hz, 1H), 6.40 (dd, J = 11.8, 9.1 Hz, 0.6H), 6.14 (dd, J = 15.8, 0.9 Hz, 0.6H), 5.97 (dd, J = 11.8, 0.8 Hz, 1H), 5.48–5.44 (m, 1H), 4.80 (d, J = 11.5 Hz, 1H), 4.68 (d, J = 11.8 Hz, 1.6H), 4.63 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 5.1 Hz, 1H), 4.59–4.57 (m, Hz, 2.4H), 4.51 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.5 Hz, 0.6H), 4.28–4.25 (m, 0.6H), 4.22 (q, J = 7.1 Hz, 1.2H), 4.17 (qd, J = 7.1, 0.9 Hz, 2H), 3.89 (dd, J = 6.0, 3.7 Hz, 1H), 3.80–3.68 (m, 3.8H), 3.66–3.61 (m, 1.6H), 1.31 (t, J = 7.1 Hz, 1.8H), 1.27 (t, J = 7.1 Hz, 3H); 13C NMR (150 MHz, CDCl₃) δ 166.0, 146.5, 145.4, 138.6, 138.5, 138.3, 138.2, 137.8, 137.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 124.0, 122.5, 81.4, 81.1, 80.2, 79.2, 78.6, 74.8, 74.6, 73.7, 73.1, 73.1, 71.6, 71.5, 61.9, 61.9, 60.7, 60.5, 14.4, 14.3; HRMS (ESI): calcd for C₃₀H₃₄O₆Na [M + Na]+ 513.2258, found 513.2258.

Ethyl 3,4,5-tri-O-benzyl-6-hydroxyshikimate (5)

A suspension of elemental selenium (1.09 g, 13.75 mmol) in anhydrous THF (250 mL) was cooled in an ice bath and n-BuLi (1.6 M in hexanes, 8.6 mL, 13.75 mmol) was added dropwise (a clear solution was produced) and the mixture was stirred for 15 min in 0 °C. After that reaction mixture was cooled to −78 °C, solution of 8 (5.60 g, 11.46 mmol in 100 mL of anhydrous THF) was added dropwise and stirring was continued through the next 30 min and then cryo-bath was removed and mixture was allowed to warm to room temperature and stirring was continued for the next 1 h. After that time, reaction was cooled to 0 °C and hydrogen peroxide (35% v/v, 10.1 mL, 114.6 mmol) and pyridine (4.6 mL, 57.3 mmol) were added. Ice bath was removed and mixture was heated to 50 °C for 1 h (solution became clear and colorless). After solvent evaporation under reduced pressure oily residue was dissolved in ethyl acetate (200 mL), washed twice with water (2 × 80 mL) and brine (100 mL) and dried over anhydrous MgSO₄. Solvent was evaporated under reduced pressure and crude product was purified by column chromatography (Hex/EtOAc 4:1 to 3:1) to give title product as colorless syrup (4.22 g, 8.65 mmol, 76%, 6s[anti]/6R[syn] 1:0.33). 1 g sample of 5 was separated by column chromatography (Hex/EtOAc 5:1 to 3:1) to give 6S)-5 (0.75 g) and (6R)-5 (0.24 g). Ethyl (6S)-3,4,5-tri-O-benzyl-6-hydroxyshikimate (6S,5): [α]20D = −73.1 (c 1.0, CHCl₃); 1H NMR (600 MHz, CDCl₃) δ 7.39–7.27 (m, 13H), 7.24–7.21 (m, 2H), 6.96 (dd, J = 2.3, 0.9 Hz, 1H), 4.77 (d, J = 11.9 Hz, 1H), 4.67 (dd, J = 11.9, 6.3 Hz, 3H), 4.63 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.50 (dd, J = 9.4, 2.8 Hz, 1H), 4.38 (t, J = 2.8 Hz, 1H), 4.29–4.22 (m, 2H), 4.05 (dd, J = 5.5, 2.9 Hz, 1H), 3.94–3.91 (m, 1H), 3.30 (d, J = 9.3 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); 13C NMR (150 MHz, CDCl₃) δ 166.0, 138.0, 137.9, 137.7, 137.4, 132.1, 128.6, 128.2, 128.1, 128.0, 127.8, 127.8, 74.3, 73.7, 73.7, 72.8, 71.9, 66.2, 61.0, 14.3; HRMS (ESI): calcd for C₁₅H₁₃O₄Na [M + Na]+ 511.2091, found 511.2091; Ethyl (6R)-3,4,5-tri-O-benzyl-6-hydroxyshikimate (6R,5): [α]20D = −82.9 (c 1.0, CHCl₃); 1H NMR (600 MHz, CDCl₃) δ 7.38–7.27 (m, 15H), 6.88 (d, J = 3.7 Hz, 1H), 4.80 (t, J = 3.2 Hz, 1H), 4.76 (d, J =
11.7 Hz, 1H), 4.73–4.66 (m, 4H), 4.62 (d, J = 11.9 Hz, 1H), 4.30 (t, J = 3.3 Hz, 1H), 4.23 (qd, J = 7.1, 1.0 Hz, 2H), 4.04 (dd, J = 7.9, 4.1 Hz, 1H), 3.94 (dd, J = 7.9, 3.7 Hz, 1H), 3.19 (d, J = 3.3 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 166.3, 138.4, 138.2, 137.9, 132.1, 128.6, 128.6, 128.5, 128.1, 128.0, 128.0, 127.8, 76.3, 75.5, 73.9, 73.4, 72.5 (2C), 65.4, 61.2, 14.3; HRMS (ESI): calcd for C30H32O6Na [M + Na]+ 511.2091, found 511.2091.

3,4,5-Tri-O-benzyl(−)-MK7607 (6R)-9

A solution of compound (6R)-5 (0.10 g, 0.2 mmol) in anhydrous methylene chloride (5 mL) was cooled to −30 °C and solution of DIBAL-H (1 M in methylene chloride, 1.2 mL, 1.2 mmol) was added dropwise. When the addition was complete, the mixture was stirred at −10 °C for 3 h. After that time, methanol (1 mL) was added to quench the reaction, and mixture was stirred at −10 °C for 30 min. After water addition (5 mL) and few drops of 1 M aqueous HCl, water phase was extracted with methylene chloride (3 × 5 mL) and combined organic phases were washed with water (2 × 5 mL) and brine (10 mL) and dried over anhydrous MgSO4. Solvent was evaporated under reduced pressure. Crude oil was purified by column chromatography (Hex/EtOAc 2 : 1 to 1 : 1) to give title compound as a colorless syrup (0.03 g, 0.067 mmol, 33%). Column chromatography (Hex/EtOAc 2 : 1 to 1 : 1) to give title compound as a colorless syrup (0.03 g, 0.067 mmol, 33%). [α]D20 = −78.5 (c 1.1, CHCl3); 1H NMR (600 MHz, CDCl3) δ 7.36–7.27 (m, 15H), 5.83 (d, J = 3.9 Hz, 1H), 4.75–4.68 (m, 4H), 4.65 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.43 (s, 1H), 4.24 (d, J = 13.4 Hz, 1H), 4.18–4.13 (m, 2H), 4.02 (dd, J = 8.2, 4.3 Hz, 1H), 3.92 (dd, J = 8.2, 3.6 Hz, 1H), 2.83 (d, J = 4.0 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 139.7, 138.5, 137.8, 128.5, 128.4, 128.0, 127.8, 127.7, 123.8, 76.7, 75.6, 73.6, 73.2, 72.2, 72.0, 67.3, 64.9; HRMS (ESI): calcd for C28H30O5Na [M + Na]+ 469.1985, found 469.1981.

6-Epi-3,4,5-tri-O-benzyl(−)-MK7607 (6S)-9

A solution of compound (6S)-5 (0.22 g, 0.45 mmol) in anhydrous methylene chloride (10 mL) was cooled to −30 °C and solution of DIBAL-H (1 M in methylene chloride, 2.7 mL, 2.7 mmol) was added dropwise. When the addition was complete, the mixture was stirred at −10 °C for 3 h. After that time, methanol (2 mL) was added to quench the reaction, and mixture was stirred at −10 °C for 30 min. After water addition (10 mL) and few drops (0.5 mL) of 1 M aqueous HCl, water phase was extracted with methylene chloride (3 × 10 mL) and combined organic phases were washed with water (2 × 10 mL) and brine (20 mL) and dried over anhydrous MgSO4. Solvent was evaporated under reduced pressure. Crude oil was purified by column chromatography (Hex/EtOAc 2 : 1 to 1 : 1) to give title compound as a white solid (0.13 g, 0.29 mmol, 65%). Mp. 82–83 °C; [α]D20 = −48.5 (c 0.65, CHCl3); 1H NMR (600 MHz, CDCl3) δ 7.38–7.27 (m, 15H), 5.81 (d, J = 1.7 Hz, 1H), 4.76 (d, J = 11.9 Hz, 2H), 4.69–4.65 (m, 4H), 4.22 (s, 3H), 4.11 (dd, J = 7.5, 4.8 Hz, 1H), 3.98 (dd, J = 7.2, 4.7 Hz, 1H), 3.79 (dd, J = 7.1, 3.6 Hz, 1H), 2.87 (d, J = 8.0 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 140.0, 138.4, 138.2, 137.9, 128.5, 128.4, 124.8, 129.7, 129.7, 127.8, 127.7, 127.7, 127.8, 78.9, 76.5, 73.5, 73.1, 72.7, 71.7, 70.1, 64.5; HRMS (ESI): calcd for C28H30O5Na [M + Na]+ 469.1985, found 469.1981.

4,5,6-Tri-O-benzyl(−)-valienamine-N-benzyl carbamate (11) and 4,5,6-tri-O-benzyl(+)β-valienamine-N-benzyl carbamate (12)

To a stirred solution of 10 (0.69 g, 0.11 mmol) in anhydrous toluene (0.74 mL) was added Na2CO3 (0.132 g, 1.25 mmol) and chlorosulfonyl isocyanate (0.07 mL, 0.83 mmol) at 0 °C under argon. The reaction mixture was stirred for 15 h at 0 °C and quenched carefully with addition H2O (1 mL). The aqueous layer was extracted with ethyl acetate (2 × 2 mL). The organic layer was added to a solution of aqueous 25% Na2SO4 (2 mL). The reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with H2O (−3 mL) and brine (−3 mL), dried over anhydrous MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography (Hex/EtOAc 7 : 1 to 4 : 1) to give title compounds 11 (0.038 g, 0.055 mmol, 51%), 12 (0.006 g, 0.01 mmol, 9%) and substrate 10 (0.013 g, 0.021 mmol, 19%) was recovered. 4,5,6-Tri-O-benzyl(−)-valienamine-N-benzyl carbamate (11): [α]D20 = −28.9 (c 1.0, CHCl3); 1H NMR and 13C NMR spectra are identical as reported in lit. for enantiomer; 1H NMR (600 MHz, CDCl3) δ 7.38–7.27 (m, 24H), 7.25 (s, 1H), 5.82 (s, 1H), 5.15–5.05 (m, 3H), 4.75 (d, J = 11.4 Hz, 1H), 4.72–4.55 (m, 6H), 4.48 (d, J = 11.8 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 4.24 (d, J = 12.1 Hz, 1H), 4.06 (d, J = 3.4 Hz, 1H), 3.91 (d, J = 12.1 Hz, 1H), 3.81 (dd, J = 7.4, 4.8 Hz, 1H), 3.77–3.71 (m, 1H); 13C NMR (150 MHz, CDCl3) δ 156.2, 138.3, 138.2, 137.9, 137.2, 136.6, 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 125.2, 76.3, 75.9, 74.3, 73.8, 72.2, 72.1, 70.6, 66.9, 47.2; HRMS (ESI): calcd for C48H40N6O4Na [M + Na]+ 692.2982, found 692.2982.

4,5,6-Tri-O-benzyl(−)-valienamine-N-benzyl carbamate (12): 1H NMR and 13C NMR spectra are identical as we previously reported; 1H NMR (600 MHz, CDCl3) δ 7.35–7.26 (m,
A solution of compound 5 (0.30 g, 0.61 mmol) in anhydrous methylene chloride (10 mL) was cooled to −30 °C and solution of DIBAL-H (1 M in methylene chloride, 3.7 mL, 3.7 mmol) was added dropwise. When the addition was complete, the mixture was stirred at −10 °C for 3 h. After that time, methanol (2 mL) was added to quench the reaction, and mixture was stirred at −10 °C for 30 min. After water addition (10 mL) and few drops (<1 mL) of 1 M aqueous HCl, water phase was extracted with methylene chloride (3 × 15 mL) and combined organic phases were washed with water (2 × 15 mL) and brine (20 mL) and dried over anhydrous MgSO4. Solvent was evaporated under reduced pressure. Crude oil was purified by column chromatography (Hex/EtOAc 2 : 1 to 1 : 1) to give title mixture of diastereoisomers as semi-solid residue (0.131 g, 0.29 mmol, 48%). Products were characterized as pure diastereoisomers (6S)-9 and (6R)-9.

A solution of mixture of compounds 9 (0.12 g, 0.27 mmol) in anhydrous methylene chloride (3 mL) was cooled to −20 °C and TBDPSCl (0.089 g, 0.32 mmol) was added in one portion followed by dropwise addition of solution of imidazole (0.045 g, 0.65 mmol in 1 mL anhydrous DMF) and stirring was continued in −20 °C for 30 min. Ice bath was removed and mixture was allowed to warm to room temperature. After addition of water (5 mL), product was extracted with EtOAc (3 × 10 mL) and combined organic layers were washed with water (2 × 10 mL), brine (15 mL) and dried over anhydrous MgSO4. After solvent evaporation, oily residue was purified by column chromatography (Hex/EtOAc 6 : 1 to 5 : 1) to give pure compound 13 (mixture of diastereoisomers) as a clear syrup (0.118 g, 0.17 mmol, 64%). 1H NMR (600 MHz, CDCl3) δ 7.70–7.63 (m, 4.84H), 7.44–7.27 (m, 25.41H), 5.96 (d, J = 4.5 Hz, 0.21H), 5.87 (d, J = 2.3 Hz, 1H), 4.82–4.63 (m, 7.26H), 4.35–4.27 (m, 2.42H), 4.20 (d, J = 20.1 Hz, 1.21H), 4.16 (t, J = 3.9 Hz, 0.21H), 4.07 (s, 1H), 4.04 (dd, J = 9.0, 4.2 Hz, 1H), 4.00 (dd, J = 7.2, 4.7 Hz, 1H), 3.94 (dd, J = 9.0, 3.8 Hz, 0.21H), 3.77 (dd, J = 7.2, 3.7 Hz, 1H), 2.69 (s, 0.21H), 2.61 (d, J = 5.6 Hz, 1H), 1.08–1.05 (m, 10.89H); 13C NMR (150 MHz, CDCl3) δ 140.0, 140.0, 138.9, 138.9, 138.7, 138.6, 138.4, 138.3, 135.7, 135.7, 134.9, 133.5, 133.5, 133.4, 129.8, 128.6, 128.5, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 121.8, 120.8, 79.4, 77.0, 76.3, 73.6, 73.2, 73.1, 72.6, 72.1, 72.0, 71.5, 69.6, 66.6, 64.8, 64.4, 27.0, 19.4; HRMS (ESI): calcd for C44H48O5SiNa [M + Na]+ 707.3163, found 707.3165.
Compound 16 was dissolved in anhydrous acetone (10 mL) and cooled to 0 °C followed by addition of NaH (1.44 g, 9.61 mmol). Reaction was stirred for 15 min in 0 °C and then heated to 40 °C for 2 h (covered with aluminum foil to avoid light access). Solvent was evaporated under reduced pressure (below 35 °C). Crude semi-solid residue was purified by flash column chromatography (Hex/EtOAc 7 : 1 to 6 : 1) to afford iodine intermediate (17) as a colorless syrup (0.376 g, 0.846, quant., 88% NMR purity). NMR (600 MHz, CDCl3) δ 4.61 (m, 4H), 4.57 (d, J = 4.35 Hz, 1H), 3.95 (dd, J = 3.95, 2.40 Hz, 1H);1H NMR (600 MHz, CD3OD) δ 3.87 (dd, J = 3.87, 2.4 Hz, 1H), 3.57 (d, J = 3.57 Hz, 1H), 2.87 (d, J = 2.87 Hz, 1H), 2.71 (d, J = 2.71 Hz, 1H);1H NMR and 13C NMR are identical as previously reported.

**Conferences of interest**

There are no conflicts to declare.

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