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## Graphical Abstract

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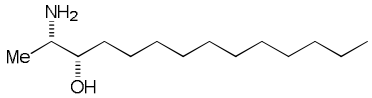

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# Asymmetric synthesis of *N*,*O*-diacetyl-3-*epi*-xestoaminol C: structure and absolute configuration confirmation of 3-*epi*-xestoaminol C

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ABSTRACT

The asymmetric synthesis of *N*,*O*-diacetyl-3-*epi*-xestoaminol C is reported. The synthesis employs diastereoselective aminohydroxylation of *tert*-butyl crotonate [conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, then *in situ* enolate oxidation with (+)-camphorsulfonyloxaziridine (CSO)] and a diastereoselective reduction protocol as the key stereodefining steps. The synthetic sample of the natural product was isolated as its *N*,*O*-diacetyl derivative for ease of purification; this material was prepared in ten steps and 17% overall yield from commercially available *tert*-butyl crotonate. This synthesis confirms unambiguously both the assigned structure and absolute (*S*,*S*)-configuration of the natural product.



The vicinal amino alcohol motif is a common sub-structure of a range of biologically active natural and non-natural products. For example in 1990, Jiménez and Crews reported the isolation of xestoaminol C from a Fijian sponge, *Xestospongia* sp., and found that it displayed reverse transcriptase inhibition.[1,2] In 2014, Keyzers and co-workers reported the isolation of the diastereoisomeric compound, 3-*epi*-xestoaminol C, from the New Zealand brown alga *Xiphophora chondrophylla*, and found that it displayed broad spectrum antimicrobial activity.[3] The structure and relative configuration of 3-*epi*-xestoaminol C was assigned by a combination of NMR spectroscopic and mass spectrometric analyses, chemical derivatisation, and comparison with data reported for xestoaminol C, whilst its absolute (*S*,*S*)-configuration was assigned by a derivatisation method[2] (Figure 1). Since its isolation, several syntheses of xestoaminol C have been reported,[4-7] including our synthesis which employed the aminohydroxylation of *tert*-butyl crotonate as the key stereodefining step.[5] The first synthesis of 3-*epi*-xestoaminol C was reported in early 2015.[8] Herein we report the application of our highly enantio- and diastereoselective aminohydroxylation reaction,[5] together with a diastereoselective reduction,[9] as the key stereodefining steps in an asymmetric synthesis of *N*,*O*-diacetyl-3-*epi*-xestoaminol C. Our synthesis also confirms the structure of the natural product and its absolute (*S*,*S*)-configuration.

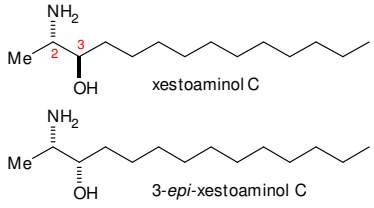


**Figure 1.** Structures of xestoaminol C and 3-*epi*-xestoaminol C.

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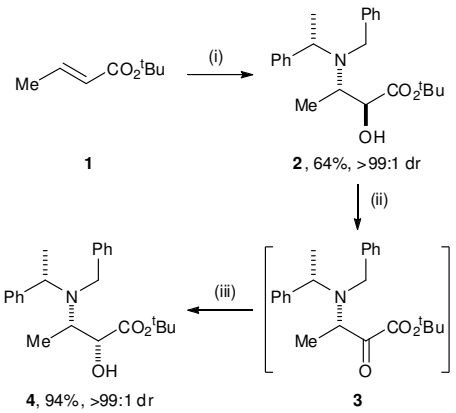
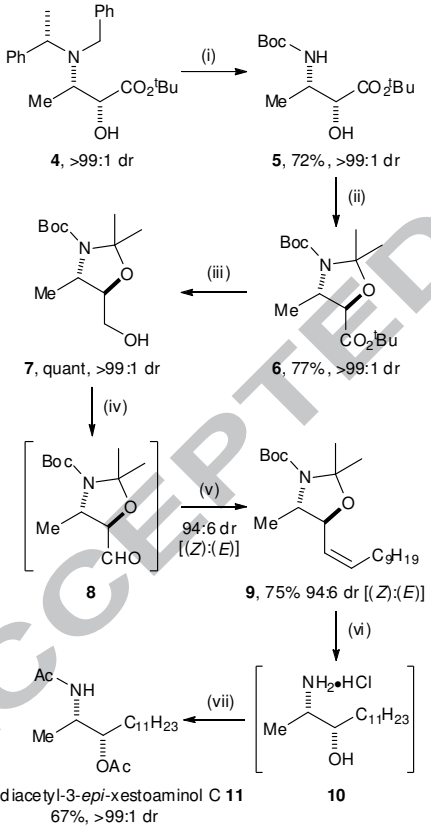
*syn*-α-Hydroxy-β-amino ester **4** was prepared from *tert*-butyl crotonate **1** (which is commercially available) using established procedures.[5,9] Diastereoselective aminohydroxylation of **1**, employing the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide followed by *in situ* enolate oxidation with (+)-camphorsulfonyloxaziridine (CSO), gave *anti*-α-hydroxy-β-amino ester **2** in 64% yield and >99:1 dr.[5,9] Oxidation of **2** under Swern conditions gave complete conversion to ketone **3**, which was reduced diastereoselectively using $NaBH_4$ in MeOH at −20 °C to give *syn*-α-hydroxy-β-amino ester **4** in 94% yield (from **2**)[9] and in >99:1 dr (Scheme 1).




**Scheme 1.** *Reagents and conditions:* (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) DMSO, $(ClCO)_2$, $Et_3N$, $CH_2Cl_2$, −78 °C to rt, 1 h; (iii) $NaBH_4$, MeOH, −20 °C, 2 h.

Based on our previously reported synthesis of xestoaminol C,[5] protecting group manipulation of **4** was next undertaken: hydrogenolysis of **4** with *in situ* *N*-Boc protection gave **5**,[9] and subsequent treatment of **5** with 2,2-dimethoxypropane and cat. $BF_3{\cdot}Et_2O$ in acetone gave *trans*-oxazolidine **6** in 55% yield (from **4**). Reduction of **6** with $LiAlH_4$ then provided alcohol **7** in quant. yield, and of sufficient purity to use directly in the next step (Scheme 2). Recrystallisation of an aliquot enabled the identity of and relative configuration within alcohol **7** to be established unambiguously via single crystal X-ray diffraction analysis,[10] with the absolute (4*S*,5*R*)-configuration following from the determination of a Flack *x* parameter[11,12] of –0.08(16) for the structure (Figure 2). The long alkyl chain was then introduced using a Wittig olefination: oxidation of alcohol **7** via a Swern protocol gave the corresponding aldehyde **8**, which was immediately treated with the ylide derived from deprotonation of commercially available (1-decyl)triphenylphosphonium bromide with BuLi to give (*Z*)-alkene **9** in 94:6 dr [(*Z*):(*E*) ratio], isolated in 75% yield (and 94:6 dr). Hydrogenation of **9** under acidic conditions also effected global *N*,*O*-deprotection to give 3-*epi*-xestoaminol C as its hydrochloride salt **10**. In order to facilitate purification and isolation, **10** was treated with $Ac_2O$ in pyridine to effect *N*- and *O*-acetylation, giving *N*,*O*-diacetyl-3-*epi*-xestoaminol C **11** in 67% yield (from **9**). This corresponds to an overall yield of 17% in ten steps from *tert*-butyl crotonate **1** (Scheme 2).




**Scheme 2.** *Reagents and conditions:* (i) $H_2$, $Pd(OH)_2$/C, $Boc_2O$, EtOAc, rt, 12 h; (ii) 2,2-dimethoxypropane, $BF_3{\cdot}Et_2O$, acetone, rt, 12 h; (iii) $LiAlH_4$, THF, 0 °C to rt, 12 h; (iv) DMSO, $(ClCO)_2$, $Et_3N$, $CH_2Cl_2$, –78 °C to rt, 1 h; (v) $[C_{10}H_{21}PPh_3]^+[Br]^-$, BuLi, THF, hexane, –78 °C to rt, 12 h; (vi) $H_2$, $Pd(OH)_2$/C, HCl (3.0 M, aq), MeOH, rt, 12 h; (vii) $Ac_2O$, DMAP, pyridine, rt, 12 h.

Excellent agreement was noted between both the $^1H$ and $^{13}C$ NMR spectroscopic data reported by Keyzers and co-workers[3] for their sample of **11** derived from the natural source with those for our synthetic sample of **11**, thus unambiguously confirming

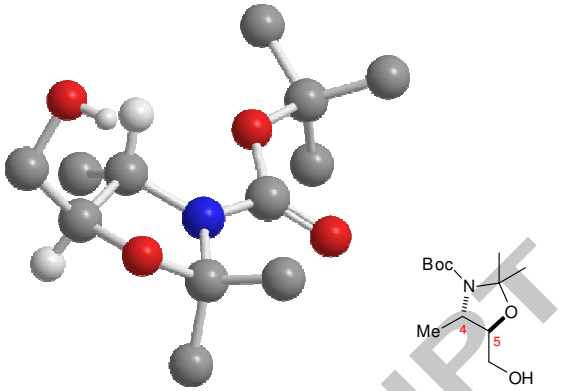
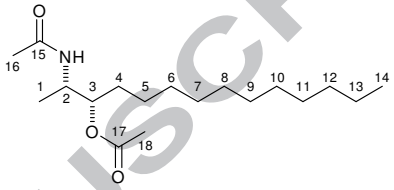



**Figure 2.** Single crystal X-ray structure of **7** (selected H atoms are omitted for clarity).




| proton # | Keyzers and co-workers $\delta_H$ (600 MHz) | This study $\delta_H$ (500 MHz) |
|---|---|---|
| 1 | 1.10 (1H, d, *J* = 6.8) | 1.11 (3H, d, *J* = 6.8) |
| 2 | 4.20 (1H, dqd, *J* = 9.3, 6.8, 4.1) | 4.21 (1H, dqd, *J* = 9.2, 6.8, 4.1) |
| 3 | 4.85 (1H, ddd, *J* = 7.6, 5.9, 4.1) | 4.87 (1H, ddd, *J* = 7.1, 5.9, 4.1) |
| 4 | 1.52 (2H, m) | 1.53 (2H, m) |
| 5–13 | 1.26 (18H, m)* | 1.28 (18H, m) |
| 14 | 0.87 (3H, d, *J* = 7.0) | 0.88 (3H, d, *J* = 7.0) |
| 16 | 1.99 (3H, s) | 2.00 (3H, s) |
| 18 | 2.09 (3H, s) | 2.10 (3H, s) |
| NH | 5.53 (1H, d, *J* = 9.3) | 5.53 (1H, d, *J* = 9.2) |

| carbon # | Keyzers and co-workers $\delta_C$ (150 MHz) | This study $\delta_C$ (125 MHz) |
|---|---|---|
| 1 | 18.7 | 18.5 |
| 2 | 47.4 | 47.2 |
| 3 | 76.6 | 76.5 |
| 4 | 31.7 | 31.6 |
| 5 | 25.4 | 25.3 |
| 6–11 | 29.5–29.8 | 29.3–29.6 |
| 12 | 32.1 | 31.9 |
| 13 | 22.8 | 22.7 |
| 14 | 14.3 | 14.1 |
| 15 | 169.6 | 169.4 |
| 16 | 23.6 | 23.4 |
| 17 | 171.7 | 170.9 |
| 18 | 21.2 | 21.0 |

**Figure 3.** $^1H$ and $^{13}C$ NMR spectroscopic data (in $CDCl_3$) for the samples of **11** derived from the natural source and the synthetic material. The numbering convention adopted by Keyzers and co-workers (Ref. 3) has also been adopted here. *Resonances corresponding to the protons of the long alkyl chain are reported at 1.24 (12H, m), 1.25 (2H, m), 1.27 (2H, m), 1.28 (2H, m); the mid-point of these has been quoted here for purposes of comparison.

both the structure of and relative configuration within the natural product. Furthermore, comparison of the specific rotation values for these two samples of **11** {$[\alpha]_D^{25}$ −23 (*c* 0.1 in $CHCl_3$) for the sample derived from the natural source[3] versus $[\alpha]_D^{25}$ −22.6 (*c* 0.5 in $CHCl_3$) for our synthetic sample} showed identical sign and very close magnitude, thus confirming unambiguously the absolute (*S*,*S*)-configuration originally assigned to the natural product by Keyzers and co-workers[3] (Figure 3).

In conclusion, we have completed an asymmetric synthesis which unambiguously confirms both the structure and absolute configuration of 3-*epi*-xestoaminol C. The synthesis employs the enantio- and diastereoselective aminohydroxylation of *tert*-butyl crotonate and a diastereoselective reduction as the key steps to install the stereogenic centers present within the target, which was isolated as the *N*,*O*-diacetyl derivative for ease of purification. The overall yield of *N*,*O*-diacetyl-3-*epi*-xestoaminol C obtained via this method was 17% over ten steps from *tert*-butyl crotonate (which is commercially available). Comparison of the $^1$H and $^{13}$C NMR spectroscopic data of this synthetic sample of *N*,*O*-diacetyl-3-*epi*-xestoaminol C with those reported for the material derived from the natural source revealed excellent agreement, thus serving to confirm both the structure and relative configuration of the natural product. Furthermore, comparison of the specific rotation values for these two samples revealed them to be of identical sign and very close in magnitude, thus enabling the absolute (*S*,*S*)-configuration of 3-*epi*-xestoaminol C, originally assigned to the natural product upon its isolation by means of a derivatisation method, to be confirmed unambiguously.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.XXXX.

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