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COMMUNICATION

Total synthesis of a cuticular hydrocarbon from the cane beetle *Antitrogus parvulus*: confirmation of the relative stereochemistry†

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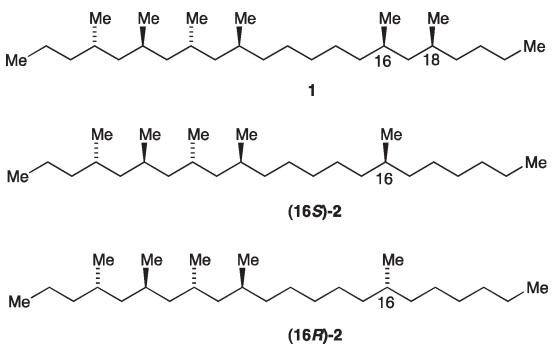
The stereoselective reaction of an allyl bromide with an aldehyde mediated by a low valency bismuth species was the key reaction in stereoselective syntheses of (4*S*,6*R*,8*R*,10*S*,16*S*)- and (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosanes. ^{13}C NMR data for these compounds confirmed that the cuticular hydrocarbon isolated from the cane beetle *Antitrogus parvulus* was the (4*S*,6*R*,8*R*,10*S*,16*S*)-stereoisomer.

Two hydrocarbons isolated from the cuticular extract of the cane beetle *Antitrogus parvulus* were identified as 4,6,8,10,16,18-hexamethyl- and 4,6,8,10,16-pentamethyl-docosanes.[1] Synthesis established the *anti*,*anti*,*anti*-configuration for the methyl bearing stereogenic centres at the 4-, 6-, 8- and 10-positions for both compounds and the *syn*-configuration for the methyl groups at the 16- and 18-positions in the hexamethyl analogue.[1] Further synthetic studies subsequently established the structure of the natural hexamethyldocosane as the (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-stereoisomer **1**.[2] However, the configuration of the pentamethyldocosane at C(16) relative to its other stereogenic centres was not confirmed, *i.e.* it was not established whether the natural pentamethyldocosane is the (4*S*,6*R*,8*R*,10*S*,16*S*)- or the (4*S*,6*R*,8*R*,10*S*,16*R*)-stereoisomer **(16*S*)-2** or **(16*R*)-2**.



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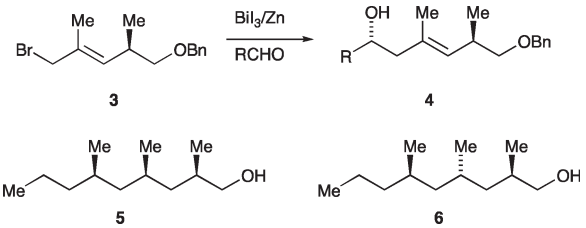
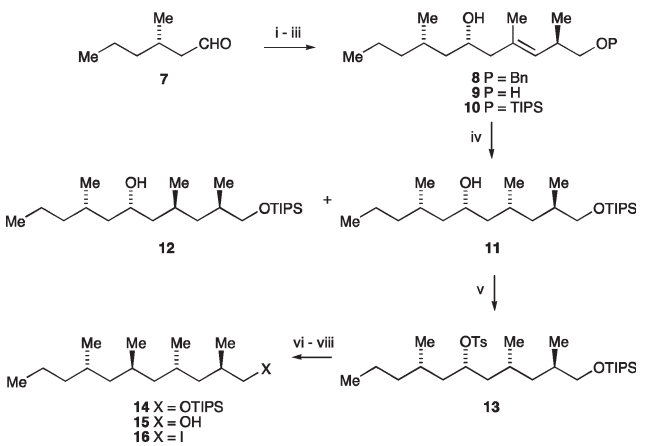
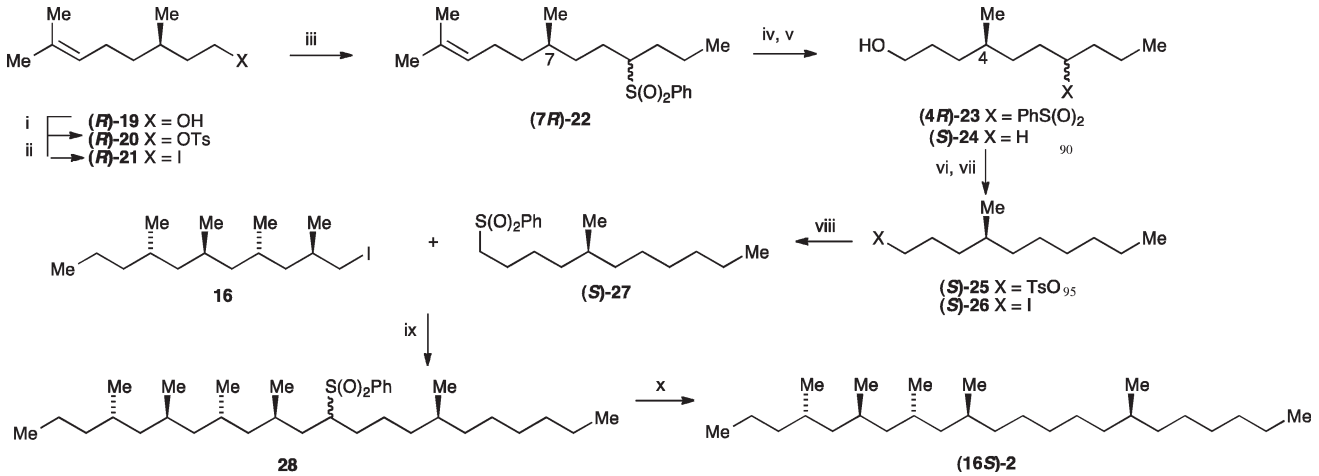
Bismuth(0) mediated reactions of 1-bromo-5-benzyloxy-2,4-dimethylpent-2-ene **3** with aldehydes give the 1,5-*anti*-(*E*)-hex-3-enols **4**.[3–5] Using stereoselective hydrogenation and cuprate based methylation with inversion, the butanal derived product (**4**, R = ^{n}Pr) was converted into the all-*syn*- or *anti*,*anti*-2,4,6-trimethylnonan-1-ols **5** and **6** with useful overall stereoselectivity.[6] We now report the stereoselective synthesis of the pentamethyldocosanes **(16*S*)-** and **(16*R*)-2** using this chemistry and confirmation that the natural product corresponds to the (16*S*)-diastereoisomer.



A synthesis of the *anti*,*anti*,*anti*-1-iodo-2,4,6,8-tetramethylundecane **16** using the organobismuth chemistry is outlined in Scheme 1. Reaction of (*S*)-3-methylhexanal **7**[7] and (4*R*,2*E*)-5-



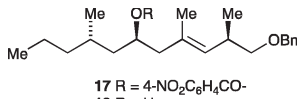
Scheme 1 Reagents and conditions: i, BiI_3, Zn powder, THF, r.t., 2 h, then add **3** and **7**, reflux, 2 h (60%); ii, Li, naph., THF, r.t., 8, −25 °C, 2 h (78%); iii, TIPSCl, imid., THF, 0 °C to r.t., 16 h (94%); iv, [Rh(NBD)diphos-4]BF_4, H_2, DCM, 950 psi, 5 h (**11**, 68%; **12**, 22%); v, TsCl, DMAP, DCM, r.t., 16 h (93%); vi, CuI, MeLi. LiI, 0 °C, add **13**, 0 °C to r.t., 16 h (21%); vii, aq. HCl, dioxane, r.t., 16 h (91%); viii, (a) TsCl, DMAP, DCM, r.t., 16 h (85%) (b) NaI, acetone.



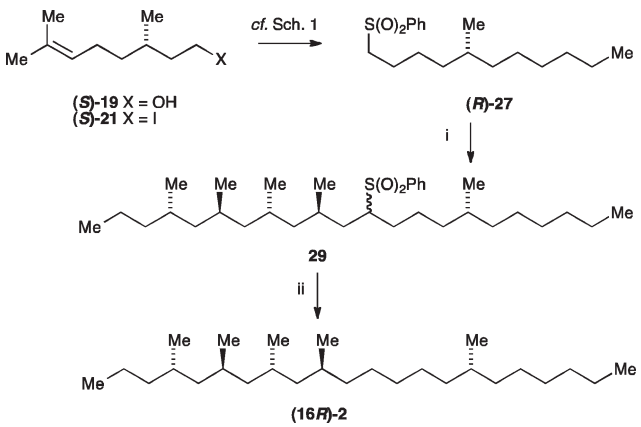
Scheme 2 Reagents and conditions: i, TsCl, DMAP, DCM, r.t., 16 h (96%); ii, NaI, acetone, reflux, 16 h (90%); iii, ^{n}BuS(O)$_2$Ph, ^{n}BuLi, DMPU, THF, −40 °C, 30 min, **(*R*)-21**, THF, −40 °C to r.t., 16 h (95%); iv, O_3, DCM, MeOH, −78 °C, then $NaBH_4$, r.t., 16 h (85%); v, Na/Hg, MeOH, r.t., 16 h (73%); vi, TsCl, DMAP, DCM, r.t., 16 h (99%); vii, NaI, acetone, reflux, 2 h (90%); viii, MeS(O)$_2$Ph, THF, DMPU, ^{n}BuLi, −40 °C, 30 min, then **(*S*)-26**, −40 °C to r.t., 16 h (73%); ix, **(*S*)-27**, ^{n}BuLi, DMPU, THF, −40 °C, 30 min, then **16**, −40 °C to r.t., 16 h (45%); x, Na/Hg, 10 equiv., MeOH, r.t., 24 h (83%).

benzyloxy-1-bromo-2,4-dimethylpent-2-ene (**3**)[6] with the low valency bismuth species prepared by treatment of bismuth(III) iodide with activated zinc in tetrahydrofuran[9] gave the 2,6-*anti*-(3*E*)-1-benzyloxy-2,4,8-trimethylundec-3-en-6-ol **8** containing only small amounts of other diastereoisomers (<10% in total). Reductive removal of the benzyl group gave the diol **9** that was protected as its monotri-*iso*-propylsilyl ether **10**. Hydroxyl directed hydrogenation using [Rh(NBD)diphos-4]BF_4 as the catalyst[10] then gave the (4*R*)- and (4*S*)-2,4,8-trimethyl-1-(tri-*iso*-propylsilyloxy)undecan-6-ols **11** and **12**, ratio *ca.* 75 : 25, which were separated by chromatography. Unfortunately, in this case, preliminary studies gave only a low yield of the 1-tri-*iso*-propylsilyloxy-2,4,6,8-tetramethylundecane **14** from the reaction of the tosylate **13** with lithium dimethylcuprate, perhaps because of steric hindrance, but rather than optimise this reaction, the silyl ether **14** that was obtained was taken through to the iodide **16** *via* the alcohol **15**[11] to complete the synthesis.

The structure of the major product **8** from the bismuth(0) mediated reaction between the aldehyde **7** and allyl bromide **3** was assigned by analogy with earlier work and was confirmed later in the synthesis. A sample of this alcohol **8** was also converted into its 2,6-*syn*-(*E*)-epimer **18** *via* a Mitsunobu reaction using 4-nitrobenzoic acid and triphenylphosphine followed by saponification of the resulting 4-nitrobenzoate **17**. The 2,6-*anti*- and -*syn*-alcohols **8** and **18** could be distinguished by ^{13}C NMR and the 2,6-*syn*-epimer **18** shown to be only a minor product (*ca.* 5%) of the organobismuth reaction.[12]



The completion of a synthesis of (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane [**(16*S*)-2**] is outlined in Scheme 2. Alkylation of n-butyl phenyl sulfone using the iodide **(*R*)-21**[13] prepared from (*R*)-citronellol [**(*R*)-19**] *via* the tosylate **(*R*)-20**[14] followed by ozonolysis of the resulting sulfone **(7*R*)-22** with a reductive work-up, gave the alcohol **(4*R*)-23**. Reductive removal of the phenylsulfonyl group, conversion of the primary alcohol **(*S*)-24**[15] into the iodide **(*S*)-26**[16] *via* toluene *p*-sulfonate **(*S*)-25**, and alkylation of methyl phenyl sulfone using this iodide gave (*S*)-5-methyl-1-phenylsulfonylundecane **(*S*)-27**. Alkylation of this sulfone using the tetramethylundecanyl iodide **16** then gave the long-chain sulfone **28** that was converted into (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane [**(16*S*)-2**] by reductive removal of the phenylsulfonyl group.



Scheme 3 Reagents and conditions: i, **(*R*)-27**, ^{n}BuLi, THF, DMPU, −40 °C, 30 min, then **16**, −40 °C–r.t., 16 h (34%); ii, Na/Hg, MeOH, r. t., 6 h (85%).

(*S*)-Citronellol [**(*S*)-19**] was converted into (*R*)-5-methyl-1-phenylsulfonylundecane **(*R*)-27** *via* (*S*)-3,7-dimethyloct-6-enyl iodide **(*S*)-21**.[17,18] Alkylation of this sulfone using the iodide **16** gave the 11-phenylsulfonyldocosane **29** that was reduced to give (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane [**(16*R*)-2**], see Scheme 3.

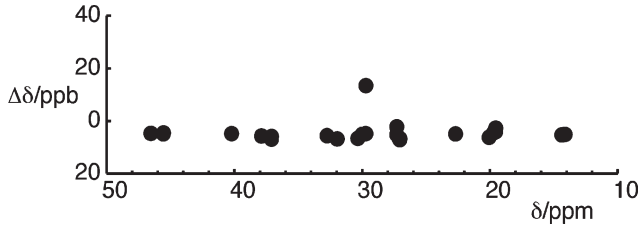


Fig. 1 Chemical shift differences in parts per billion between **(16*S*)-2** and the natural product.

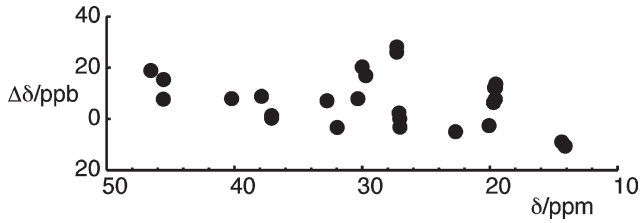


Fig. 2 Chemical shift differences in parts per billion between **(16*R*)-2** and the natural product.

Having prepared the pentamethyldocosanes **(16*S*)-** and **(16*R*)-2**, it remained to establish which diastereoisomer corresponded to the natural product. Unfortunately, no sample of the natural product was available and its optical rotation was unknown, and so it was necessary to compare the ^{13}C NMR data of the two epimers **(16*S*)-2** and **(16*R*)-2** with the data available for the natural product. As the ^{13}C NMR spectra of the two epimers were very similar indeed,[1] a quantitative comparison was used. Fortunately the original data were measured at high field (17.6 T) and reported to 1 ppb precision, so spectra measured at 9.4 T were processed with Gaussian weighting and extensive zero filling to allow detailed comparison.

Fig. 1 shows the differences in the chemical shifts between those listed[1] for the natural product and our data for the (16*S*)-epimer **(16*S*)-2**. Apart from the peak assigned to C(19),[19] all the peaks correspond to within less 5 ppb once the small difference in referencing is corrected for, with an rms error of 1.4 ppb (less than the instrumental linewidth).

In contrast, the differences between the chemical shifts listed for the natural product and our data for the (16*R*)-epimer **(16*R*)-2**, are much larger, with an rms error of 10 ppb (see Fig. 2). Based on this comparison, the natural product was identified as (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **(16*S*)-2**.[20]

Of interest in this work is the use of the allyl organobismuth chemistry for the stereoselective synthesis of the undecenol **8**, the confirmation of the relative stereochemistry of the naturally occurring 4,6,8,10,16-pentamethyldocosane as the (4*S*,6*R*,8*R*,10*S*,16*S*)-epimer **(16*S*)-2**, and the unusually detailed numerical comparison of the ^{13}C spectra of the natural product and the (16*S*)- and (16*R*)-epimers which allowed the assignment of stereochemistry to be made. Indeed the spectra of the natural product and the synthetic (16*S*)-epimer were, with the one exception noted, remarkably consistent.

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Notes and references

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19 In the ^{13}C NMR spectrum of the natural product, the peak at δ 29.712 was originally assigned to both C(4) and C(19) but C(19) has since been reassigned to a peak at δ 29.697 although this peak was partly obscured by an impurity in the natural product. (Personal communication from Professor W. Kitching.) However, it remains slightly more than 5 ppb different from the peak at δ 29.6987 assigned to C(19) in **(16*S*)-2** and from the peak at δ 29.6951 assigned to C(19) in the ^{13}C NMR spectrum of **(16*R*)-2**.
20 This work establishes the relative configuration of the natural 4,6,8,10,16-pentamethyldocosane. As the optical rotation of the natural hydrocarbon is unknown, the absolute configuration shown was provisionally assigned by analogy with that of the naturally occurring 4,6,8,10,16,18-hexamethyldocosane **1** (see ref. 2).