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Efficient and Selective Synthesis of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-Hexamethyldocosane via Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction)

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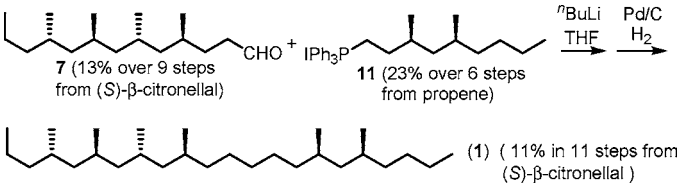
ABSTRACT



(*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-Hexamethyldocosane (1) was synthesized in 11% yield in 11 steps in the longest linear sequence from ≥98% pure (*S*)-*β*-citronellal and 6 additional steps for the preparation of 11 in 23% yield from propene. Five of the six asymmetric carbon centers were generated catalytically and stereoselectively by the ZACA reaction (5 times), one lipase-catalyzed acetylation, and two chromatographic operations.

(*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-Hexamethyldocosane (**1**) was isolated from the cuticula of the cane beetle *Antitrogus parvulus* by Kitching and co-workers[1] and shown by them to incorporate a rare *anti-anti-anti*-4,6,8,10-methyl tetrad along with a more usual *syn*-methyl diad.[2] On the basis of the deduced stereochemistry, Breit[3] and then Burgess[4] reported total syntheses of this hydrocarbon, which established the 4*S*,6*R*,8*R*,10*S*,16*R*,18*S* absolute configuration of **1**. Our recent development of an efficient and enantio-face selective ZACA route[5,6] to deoxypolypropionates, which has been shown to favor the sy*n* relationship between two neighboring methyl groups,[6a−6c] vis-à-vis the unusual anti-anti-anti configuration found in **1** prompted us to attempt the synthesis of **1** by the ZACA route, in part, for exploring its scope and limitations. It should be clearly noted that

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(2) For a recent overview of deoxypolypropionates, see: Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, 1057−1076.

(3) (a) Herber, C.; Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5267−5269. (b) Herber, C.; Breit, B. *Eur. J. Org. Chem.* **2007**, 3512−3519. (c) For a related methodological study, see: Breit, B. *Angew. Chem., Int. Ed.* **1998**, *37*, 525−527.

(4) (a) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391−1393. (b) For a related methodological study, see: Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129−1131.

(5) ZACA stands for Zr-catalyced asymmetric carboalumination of alkenes. For the discovery and early development of the ZACA reaction, see: (a) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771−10772. (b) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577−1578. (c) Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253−3256. (d) Huo, S.; Shi, J.; Negishi. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2141−2143.

(6) For applications of the ZACA reaction to asymmetric syntheses of natural products, see: (a) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782−5787. (b) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2911−2914. (c) Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E. *Org. Lett.* **2004**, *6*, 1425−1427. (d) Novak, T.; Tan, Z.; Liang, B.; Negishi, E. *J. Am. Chem. Soc.* **2005**, *127*, 2838−2839. (e) Liang, B.; Novak, T.; Tan, Z.; Negishi, E. *J. Am. Chem. Soc.* **2006**, *128*, 2770−2771. (f) Tan, Z.; Liang, B.; Huo, S.; Shi, J.; Negishi, E. *Tetrahedron: Asymmetry* **2006**, *17*, 512−515. (g) Huang, Z.; Tan, Z.; Novak, T.; Zhu, T.; Negishi, E. *Adv. Synth. Catal.* **2007**, *349*, 539−545. (h) Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771−2774. (i) Liang, B.; Negishi, E. *Org. Lett.* **2008**, *10*, 193−195.

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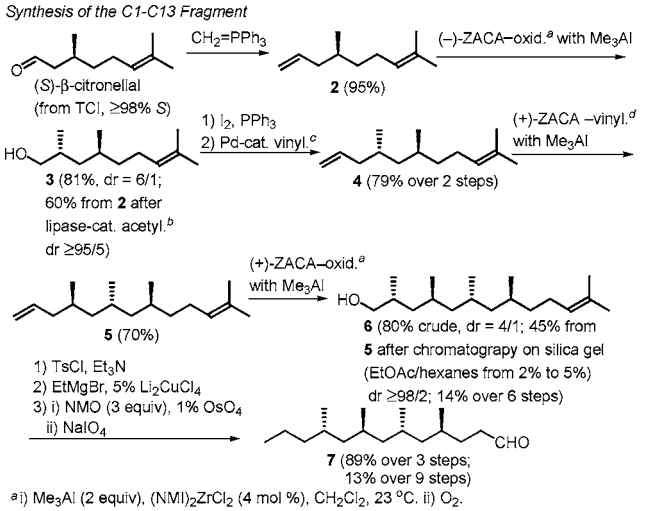
diastereoselective construction of deoxypolypropionates relying on pre-existing chiral centers[7] gives predominantly syn isomers and is hence not practical for the synthesis of anti deoxypolypropionates, such as **1**. Despite high yields and enantioselectivity figures, the use of the stoichiometric amounts of relatively expensive chiral reagents[8] becomes increasingly undesirable as the number of asymmetric carbon centers in a molecule increases. With these considerations in mind, a predominantly catalytic asymmetric synthesis of **1** has been devised as outlined in Schemes 1 and 2.

Scheme 1

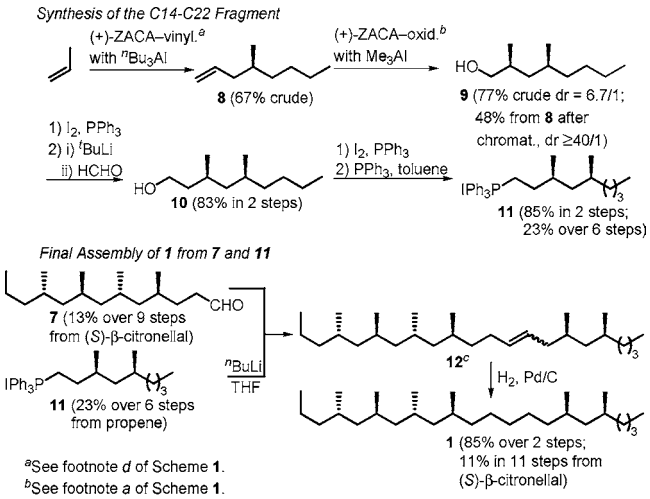


[a] i) Me_3Al (2 equiv), $(NMI)_2ZrCl_2$ (4 mol %), CH_2Cl_2, 23 °C. ii) O_2.
[b] Amano PS lipase (30 mg/mmol), vinyl acetate (5 equiv), CH_2Cl_2.
[c] i) ^{t}BuLi, ether, –78 °C. ii) dry $ZnBr_2$, THF. iii) CH_2=CHBr (3 equiv), $Pd(PPh_3)_4$ (2 mol %).
[d] i) Me_3Al or ^{n}Bu$_3$Al (2 equiv), $(NMI)_2ZrCl_2$ (3 mol %), CH_2Cl_2. ii) Evaporation of CH_2Cl_2 and Me_3Al. iii) dry $Zn(OTf)_2$ (1 equiv), DMF, 2 h, 70 °C. iv) $Pd(DPEphos)Cl_2$ (3 mol %), DIBAL-H (6 mol %), CH_2=CHBr (3 equiv), DMF.

For the preparation of the tetramethylundecane fragment, we initially opted for a fully reagent-controlled protocol involving four ZACA reactions to synthesize 2,4,6,8-tetramethyl-1-undecanol (**13**) from propene, as shown in Scheme 3. This synthesis did work very efficiently as planned. However, the anticipated low diastereomeric ratios ranging from 3.5/1 to 4.5/1 and the unfavorable chromatographic recoveries of 47−54% for improving the diastereomeric ratio to 40 or higher led to the total yield of 7% over 6 steps.

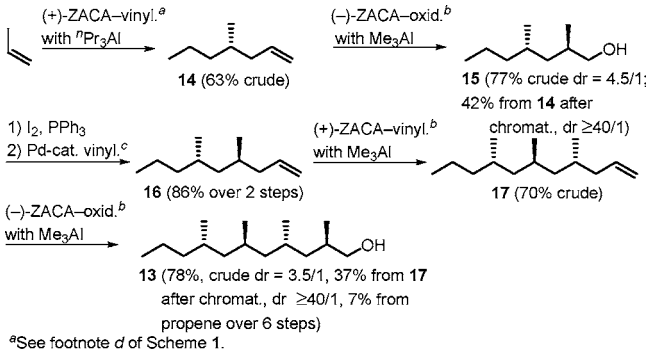
To alleviate the difficulty stemming from the generally unfavorable construction of a series of three *anti*-1,3-dimethylpropylidine moieties, the use of (*S*)-*β*-citronellal was considered as a relatively inexpensive ($453/mol from TCI) source of an enantiomerically pure (≥98% *S*) monochiral building block, which led to the synthesis of **6** (dr ≥98/2)

Scheme 2



[a] See footnote *d* of Scheme **1**.
[b] See footnote *a* of Scheme **1**.
[c] The crudely isolated **12** was characterized by comparison of its ^{1}H NMR spectra with that of pure **12** prepared via Pd-catalyzed cross-coupling reaction (see text).

Scheme 3



[a] See footnote *d* of Scheme **1**.
[b] See footnote *a* of Scheme **1**.
[c] See footnote *c* of Scheme **1**.

in 14% yield over 6 steps from (*S*)-*β*-citronellal (Scheme 1). By taking advantage of the facts that the starting (*S*)-*β*-citronellal was ≥98% *S* and that **3** was the 2*R* isomer of a 2-methyl-substituted terminal alcohol, purification of **3** was achieved by Amano PS lipase-catalyzed acetylation[6g] leading to a considerably higher recovery of 74% than that observed in the chromatographic purification (∼50% recovery). For the syntheses of shorter *syn*-dimethylalkyl derivatives **9**−**11**, a fully catalytic and reagent-controlled enantio-face selective ZACA route shown in Scheme 2 proved to be highly efficient, even though there still exists considerable room for improvement in both product yield and stereoselectivity. With the two key intermediates **7** and **11** in hand as isomerically pure compounds, the final assembly of the target compound **1** was achieved in 85% in 2 steps via Wittig olefination and catalytic hydrogenation with H_2 over Pd/C (Scheme 2). The desired product **1** thus obtained exhibited the ^{1}H and ^{13}C NMR spectra as well as $[\alpha]_D^{23} = +10.9$ (*c*, 1.5, $CHCl_3$) that were in good agreement with those reported previously.[1,3,4]

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(8) (a) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290−5313. (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081−1084. (c) Myers, A. G.; Yang, B. H.; Chen, H.; Mckinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. (d) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 457−459. (e) Birkbeck, A. A.; Enders, D. *Tetrahedron Lett.* **1998**, *39*, 7823−7826. (f) Nicolos, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766−770. (g) Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217−3220.

In summary, (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-hexamethyldocosane (**1**) was synthesized in 11% yield in 11 steps in the longest linear sequence from ≥98% pure (*S*)-*β*-citronellal. Additionally, the preparation of **11** in 26% yield over 6 steps from propene was required, making the total number of steps 17. Five of the six asymmetric carbon centers were generated in a catalytic and enantio-face selective manner using the ZACA reaction. In addition to the use of one lipase-catalyzed acetylation, just two ordinary chromatographic purifications were used to obtain the five asymmetric carbon centers with the correct absolute configurations as stereoisomerically pure chiral moieties. This predominantly catalytic and enantio-face selective ZACA-based synthesis of **1** is highly efficient. However, its cost-turnover factor needs to be further investigated and improved. Most critically, relatively low product yields stemming largely from the modest enantio-face selectivity in the ZACA reaction must be improved mainly through catalyst optimization, and such efforts are currently in progress.

At the end of this report, brief comments on the two previous syntheses of **1**[3,4] might be in order. In Breit's high-yielding synthesis, **1** was obtained in astounding 34% yield from the Me ester of (*S*)-2-methyl-3-hydroxypropionic acid, so-called (*S*)-"Roche ester", in 13 steps in the longest linear sequence via Cu-catalyzed cross-coupling of the triflate of 2,4,6,8-tetramethyl-1-undecanol with the Grignard reagent derived from 1-bromo-5,7-dimethylundecane, which was prepared in 8 steps also from (*S*)-"Roche ester". The four other asymmetric carbon centers were established off the main synthetic sequences in 3 to 4 steps each. Thus, the total number of synthetic steps must be at least 31. Its major drawback is the stoichiometric use of relatively expensive "Roche ester" twice and surprisingly expensive *o*-diphenylphosphinobenzoic acid ($9,000/mol, Aldrich) four times for the introduction of all six asymmetric carbon centers. In this respect, catalytic asymmetric hydrogenation used in Burgess' synthesis of **1**[4] is a fundamentally promising method, provided that the cost-turnover factor can be made realistically attractive. Although it is somewhat difficult to collect all pertinent details from the Burgess reports,[4] it can be discerned that the overall number of synthetic steps must exceed 30. Another fundamentally promising catalytic method involving a Cu-catalyzed asymmetric conjugated addition that has been applied to the synthesis of deoxypolypropionates[9] (but not to that of **1**) is also noteworthy, although its cost-turnover number profile appears to require further improvement as in the other cases.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of the isolated pure compuonds. This material is available free of charge via the Internet at http://pubs.acs.org.

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