Pergamon

Tetrahedron Letters, Vol. 37, No. 39, pp. 7127-7128, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01557-2

A Short and Selective Synthesis of *(S)*-geranylcitronellol via conjugate Addition of a Functionalized Copper Reagent to 2-substituted *exo*-Bornyl Crotonates[1]

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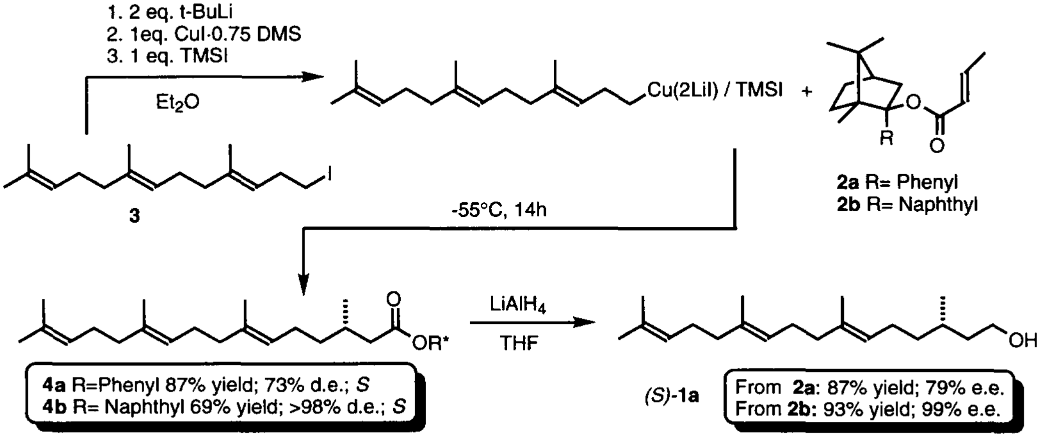
Abstract: An asymmetric synthesis of the diterpene *(S)*-geranylcitronellol **1a** and its acetate **1b** is reported. The chirality is induced by TMSI-promoted conjugate addition of a homoallylic monoorganocopper reagent to 2-naphthyl-*exo*-bornylcrotonate, which proceeds with more than 98% diastereomeric excess.

Male bumblebees of the genera *Bombus* and *Psithyrus* in Scandinavia produce a marking pheromone secretion containing geranylcitronellol, **1a**[2] and geranylcitronellyl acetate **1b**. Previous work in this laboratory has demonstrated the utility of 2-substituted *exo*-bornyl crotonates **2** as vehicles for asymmetric induction in conjugate additions of organocopper reagents,[3] including cuprates ($R_2CuLi(LiI)$) and iodotrimethylsilane promoted monoorganocopper reagents (RCu(LiI)-TMSI).[4] Recently, the reagent has been extended to conjugate adddition of acetylenic copper compounds,[4c] but other functionalized organocopper compounds together with TMSI have not previously been examined.



Scheme 1

In this paper, we report a synthetic application of a TMSI-promoted conjugate addition of a monoorganocopper reagent to 2-substituted *exo*-bornyl crotonates **2** in an asymmetric synthesis of *(S)*-geranylcitronellol **1a** and its acetate **1b**. (**Scheme 1**) [5] The homoallyliodide **3**[6] was lithiated with *tert*-butyllithium (*t* -BuLi).[7,8] The asymmetric induction with the homoallylcopper/TMSI reagent was comparable to prior observations with butylcopper/TMSI.[3a,b] Stereoselectivity and configuration [9] were determined with NMR-spectroscopy. Reduction of the esters **4a** and **4b** with $LiAlH_4$ furnished the alcohol *(S)*-**1a** in good yields.[10] The optical purity of *(S)*-**1a** confirmed the NMR-measurements of the asymmetric induction in conjugate addition to esters **2a** and **2b**. Treatment of alcohol **1a** with BuLi followed by acetyl chloride in

THF[11] afforded the *(S)*-acetate **1b**.[12] Using the phenylsubstituted bornyl crotonate **2a** and a cuprate ($R_2CuLi(3LiI)$) derived from iodide **3** gave 56% yield and a meagre 21% d.e. of the *(R)*-diastereomer. When instead the naphthylsubstituted crotonate **2b** was used, the yield was only 30% and a 56% d.e. of the *(S)*-diastereomer was observed, *i.e.* the same diastereomer obtained from TMSI/monoorganocopper. Previous experiments[3a] have shown that the induced chirality of the β-carbon is sensitive to the exact composition of the copper reagent when the RLi/Cu ratio is increased. A more reliable way to prepare the *(R)*-enantiomer of **1a** is without doubt to use a TMSI-promoted monoorganoopper reagent and the opposite enantiomer of **2b**, which can be prepared from commercially available (-)-camphor.

Acknowledgement. AJ and TO wish to thank the Carl Trygger Foundation and AB Astra Hässle for financial support. GB acknowledges financial support from the Swedish Natural Research Council (NFR) and collaboration with P. Bergman and M. Appelgren. We are grateful to Akzo Nobel AB for a generous gift of ethylene oxide.

References and notes

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5. The reaction was carried out under an atmosphere of argon. Experimental procedure: 795 mg (2.3 mmol) oxygen-free homoallylic iodide **3** was dissolved in 8 ml of ether and cooled to -110°C. To this was added 3.40 ml (2.1 equiv.) of a 1.435 M solution of *t*-BuLi. The mixture was stirred at -110°C for ca 5 minutes after which the temperature was raised to -78°C and stirred for 30 minutes. The cooling bath was removed and the reaction was allowed to warm to room temperature to remove excess *t*-BuLi. After ca 30 minutes the solution was again cooled to -78°C and added via cannula to a -78°C slurry of 544 mg CuI·0.75 DMS[4a] (2.3 mmol) in 8 ml of ether. The obtained reaction mixture was stirred for -78°C at 10 minutes, during which time the colour changed from intensely yellow to orange and finally brown. The reaction mixture was stirred at 50°C for 10 minutes, cooled to -78°C and 0.33 ml of TMSI (2.3 mmol) was added neat. Immediately after was added 160 mg (0.46 mmol) 2-naphthyl-*exo*-bornylcrotonate **2b** in 3 ml of ether. The reaction was stirred at -55°C for 14 hours and quenched with 2 ml of dry pyridine at this temperature. After 5-10 minutes at low temperature, 4 ml of ammonia/ammonium chloride buffer was added and the cooling bath was removed. The phases were separated and the ether was washed with 3x20 ml of 10% $CuSO_4$ and 20 ml of brine. The organic phase was dried over Na_2SO_4 and evaporated. Flash chromatography (R_f=0.34, 5% ether/pentane, 6 g silica gel) gave 180 mg (69%) homoallyladduct **4b**.
6. The iodide **3** was prepared following a route reported for homoallylic bromides: Bury, P.; Hareau, G.; Kocienski, P.; Dhank, D. *Tetrahedron* **1994**, *50*, 8793-8808. For other syntheses of **3**, see a. Dodd, D.S.; Oehlschlager, A.C. *J. Org. Chem.* **1992**, *57*, 2794-2803. b. Kocienski, P.; Wadman, S. *J. Org Chem.* **1989**, *54*, 1215-1217.
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9. The d.e.'s were determined by measuring the peak heights of comparable signals from the diastereotopic α-protons in esters **4a** and **4b**. Using RCu(2LiI)-TMSI, only one diastereomer of **4b** could be observed, whereas in the NMR-spectra of **4b** from the cuprate additions, two sets of well resolved signals were present. The shifts of the α-protons agreed well with corresponding signals in the spectra of the butyladducts[3b] and the same chirality of the β-carbon was assumed. After reduction, the configuration was confirmed by the sign of the optical rotation of the alcohols.[2c]
10. Spectral data for **1a**: ^{1}H-NMR ($CDCl_3$, ppm): 5.10 (m, 3H), 3.68 (m, 2H), 2.14-1.90 (m, 10H), 1.68 (bs, 3H), 1.60 (bs, 9H), 1.46-1.12 (m, 5H), 0.91 (d, 3H, J= 6Hz). ^{13}C-NMR ($CDCl_3$, ppm): 136.00, 135.07, 131.32, 124.76, 124.57, 124.39, 61.42, 40.10, 39.93(2C), 37.41, 29.41, 27.00, 26.82, 25.93, 25.57, 19.77, 17.91, 16.24, 16.20. CI-MS (NH_3): Calculated for $C_{20}H_{37}O$ (M+1): 293.284 Found: 293.283 $[\alpha]^{20}_D$ -3.56°(CH_2Cl_2) (Lit.[2c] $[\alpha]_D$ -3.60°).
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12. Spectral data for **1b**: ^{1}H-NMR ($CDCl_3$, ppm): 5.10 (m, 3H), 4.09 (m, 2H), 2.12-1.90 (m, 10H), 2.39 (s, 3H), 1.68 (bs, 3H), 1.60 (bs, 9H), 1.62-1.52 (m, 2H), 1.48-1.14 (m, 3H), 0.91 (d, 3H, J= 5.8Hz). ^{13}C-NMR ($CDCl_3$, ppm): 171.40, 135.16, 135.11, 131.44, 124.61, 124.56, 124.37, 63.24, 39.94(2C), 37.18, 35.61, 29.70, 26.96, 26.83, 25.92, 25.49, 21.27, 19.63, 17.91, 16.22, 16.21. CI-MS (NH_3): Calculated for $C_{22}H_{38}O_2$ (M^+): 334.287 Found: 334.284 $[\alpha]^{20}_D$ -2.38° (CH_2Cl_2)

(*Received in UK* 10 *May* 1996; *revised* 5 *August* 1996; *accepted* 9 *August* 1996)