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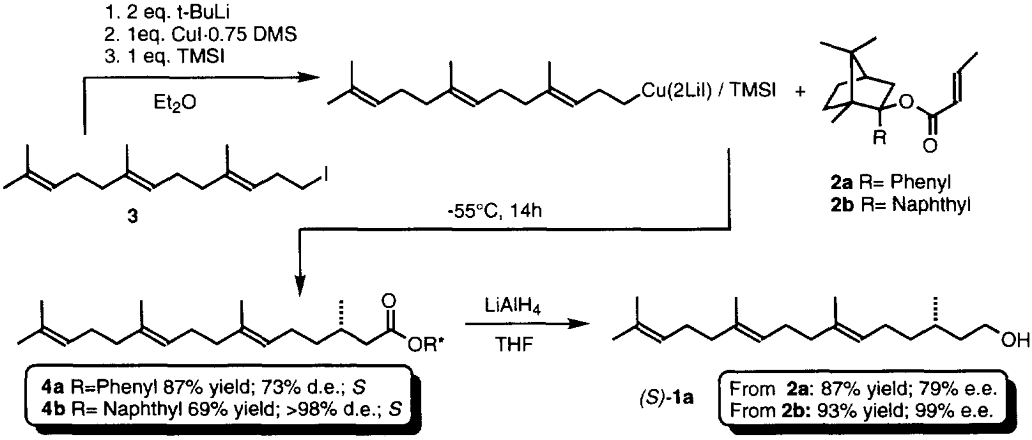
Abstract: An asymmetric synthesis of the diterpene *(S)*-geranylcitronellol **1a** and its acetate **1b** is reported. The chirality is induced by TMSI-promoted conjugate addition of a homoallylic monoorganocopper reagent to 2-naphthyl-*exo*-bornylcrotonate, which proceeds with more than 98% diastereomeric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

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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)

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