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ASYMMETRIC ADDITIONS OF 1-ALKENYLCOPPER REAGENTS TO CHIRAL ENOATES: ENANTIOSELECTIVE SYNTHESIS OF CALIFORNIA RED SCALE PHEROMONE [1].

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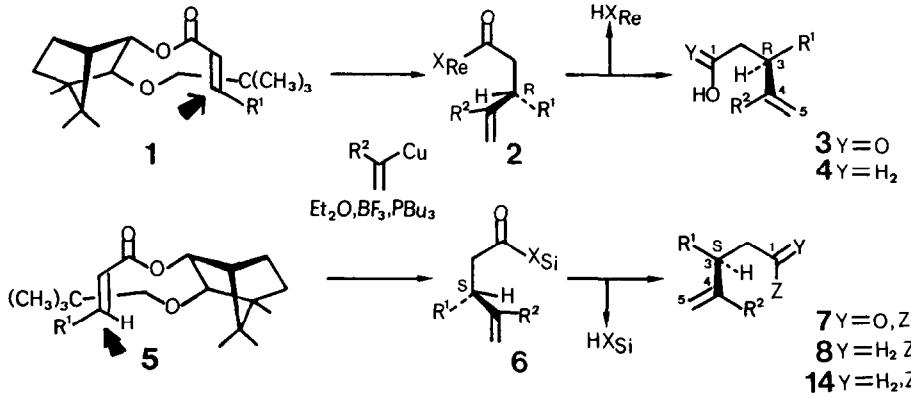
Abstract: nBu$_3$P-stabilized 1-alkenylcopper reagents undergo efficient 1,4-additions to enoates 1 and 5. Thus, acids 3, 7 or alcohols 4, 8 were obtained in high e.e. with recovery of the auxiliary. 4d was converted to pure (-)-pheromone 13, and 8b gave bromide 14b.

β-Substituted γ,δ-unsaturated carboxylic acids 3 and 7 are important building blocks for the syntheses of enantiomerically pure, complex molecules since the chiral center C(3) may induce the topicity of various functionalizations at C(1), C(4) and C(5). Both the acids 3a and 7b have served as versatile starting materials for the syntheses of lasalocid-A [2a], monensin [2b] and eldanolide [2c]. Based on previous work showing high π-face differentiation in the BF_3-promoted conjugate addition of alkylcopper reagents to chiral enoates 1 and 5 [3] we envisioned the preparation of enantiomerically pure acids 3 and 7 *via* the analogous addition of 1-alkenylcopper reagents. Our results are summarized in the Schemes 1,2 and the Table [4].

Scheme 1

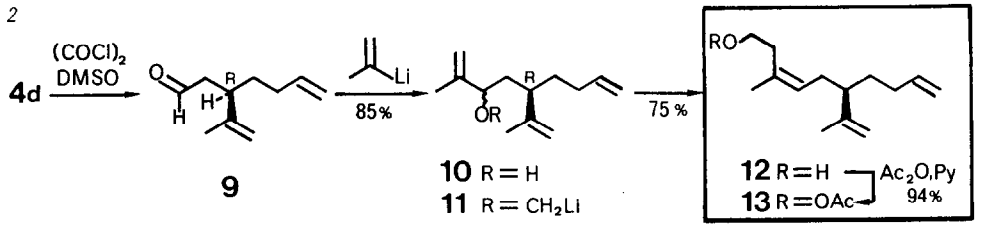


The starting (E)-enoates 1 and 5 were readily obtained upon heating the corresponding Cβ-*Re*- or Cβ-*Si*-directing auxiliary alcohol HX_{Re} or HX_{Si} [5] with the appropriate acid chloride [6] and AgCN in benzene. Treatment of enoates 1 or 5 with CH_2=CRCu.PnBu$_3$.BF_3 [7] (7eq) at -78° to -40° followed by selective oxidation of the phosphine with MCPBA (1.2eq, r.t.) and chromatography furnished adducts 2 or 6 in good yields. Saponification of esters 2 and 6 (NaOH,aq.EtOH) afforded acids 3 and 7, respectively (92-96% yield) with recovery of the auxiliary alcohol. The absolute configurations and high enantiomeric purities (94 to 99% e.e) of acids 3 and 7 were established by chiroptic comparison and by analyses (HPLC, GC, ^{1}H-NMR) of the corresponding (R)-1-(1-naphthyl)ethyl amides. Adduct 2d, thus obtained, was converted into the California red scale pheromone 13 as follows.

Table: Asymmetric Syntheses of γ,δ-Olefinic Carboxylic Acids 1 → 2 → 3 and 5 → 6 → 7.

Entry	Enoate	Resident Group R^1	1-Alkenyl-Cu R^2	Adduct	Yield%	Carboxylic Acid	e.e.%
a	1	CH_3	H	2	85	3	94.0
b	5	CH_3	H	6	85	7	94.0
c	1	CH_3	CH_3	2	86	3	99.0
d	1	CH_2=CH-$(CH_2)_2$-	CH_3	2	89	3	98.2

Scheme 2



Reduction of 2d with $LiAlH_4$ furnished the auxiliary HX_{Re} (92%) and the (R)-dienol 4d[4] (96%) which was oxidized with $(COCl)_2$/DMSO to give aldehyde 9 [4] (85%). Treatment of 9 with 2-propenyllithium in Et_2O at -78° furnished allylic alcohol 10 (85%, diastereo-isomer mixture) which was subjected to *Still's* Z-selective version of the *Wittig* rearrangement [8]. O-Alkylation with KH/iodomethyltributyltin (1eq,r.t.) and transmetalation with *n*BuLi (1.05 eq, -78°) gave *via* 11 the homoallyl alcohol 12 (72.4%(Z)/2.6%(E)). Acetylation of crude 12 (Ac_2O, pyridine,r.t.) afforded a 96.5:3.5-Z/E mixture of 13 (94%). Removal of the very minor E-isomer by preparative HPLC furnished pure (Z)-pheromone 13 ($[\alpha]_D$=-7.14°(c=2.1, $CHCl_3$)). Synthetic 13 was shown to be identical (HPLC, IR, NMR, MS) to a sample ($[\alpha]_D$=-6.95°(c=-1.6, $CHCl_3$)) obtained by separation of (R)-13 (Z/E=1:1) which was kindly provided by *R.J.Anderson*.

The above synthesis of 13 compares favorably with other approaches to this pheromone [8,9] thus illustrating the potential of asymmetric RCu/enoate additions. The utility of this process is further highlighted by the conversion of alcohol 8b to bromide 14b [2a] a precursor for the syntheses of (-)-patchoulol [10], and, as described in the following communication, of enantiomerically pure (+)-α- and (+)-δ-skytanthine and (+)-iridomyrmecin .

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