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ASYMMETRIC MICHAEL ADDITION OF A CHIRAL ESTER-DIENOLATE: ENANTIOSELECTIVE SYNTHESIS OF (-)-KHUSIMONE[1]

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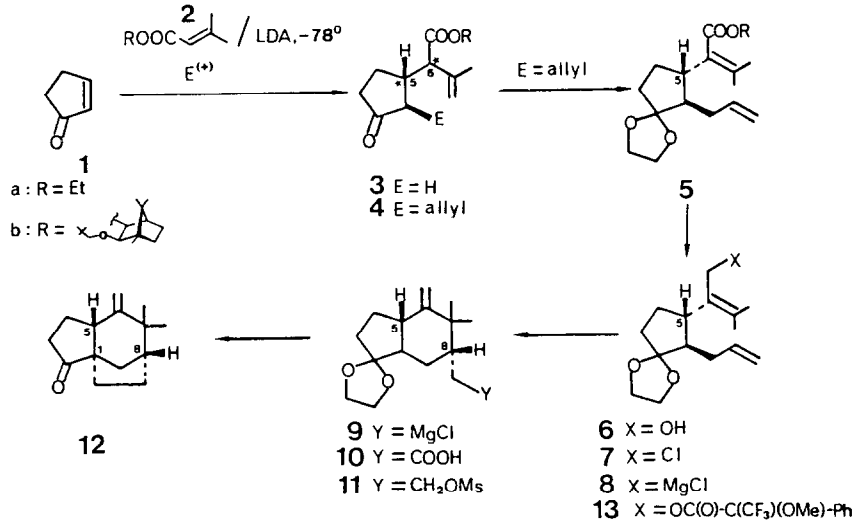
Abstract: A double π-face-selective aprotic Michael addition of the lithium dienolate derived from the chiral senecioate 2b to cyclopentenone coupled with recovery of the auxiliary 14 serves for the enantioselective synthesis of (-)-khusimone (12) (Schemes 1 and 4).

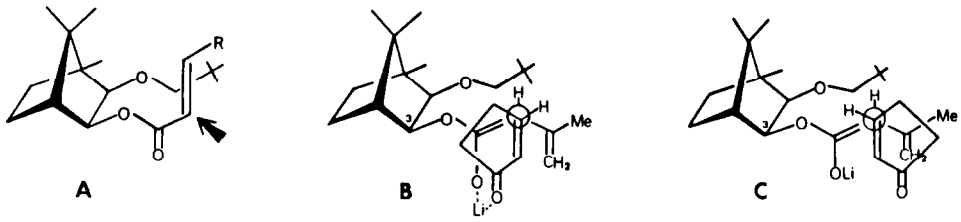
The norsesquiterpene (±)-khusimone 12 has been prepared recently *via* a remarkably regio- and stereoselective intramolecular type-II magnesium-ene reaction 8 → 9 (Scheme 1)[2]. Interested in rendering this approach enantioselective we focussed our attention on the dienolate addition/

Scheme 1



alkylation 1 → 4 where the first chiral center C(5) is created. Our strategy to control its absolute configuration was based on the following observation: addition of the dienolate derived from 2a at -78° in THF followed by either rapid protonation or alkylation of the intermediate enolate gave 3a[3] (70% yield) or 4a (56%), respectively, both with 88:12-diastereoregulation of C(6)/C(5). Accordingly a high dienolate-π-facial differentiation in the process 1 → 4 should govern the chirality of both C(6) and C(5). By analogy to the powerful topological bias observed in the Lewis-acid mediated additions to the enoates A[4] we expected selective neopentyloxy-shielding of one dienolate π-face in the enone addition B or C (Scheme 2). Rotation around the dienolate C,O-bonds should be restricted owing to the preferred synplanarity of the C(3)-H and the C-OLi bonds; this conformational hypothesis is supported by asymmetric alkylations of camphor-derived propionate enolates, as reported by *Helmchen*[5]. To predict the topicity of the conjugate addition the

Scheme 2

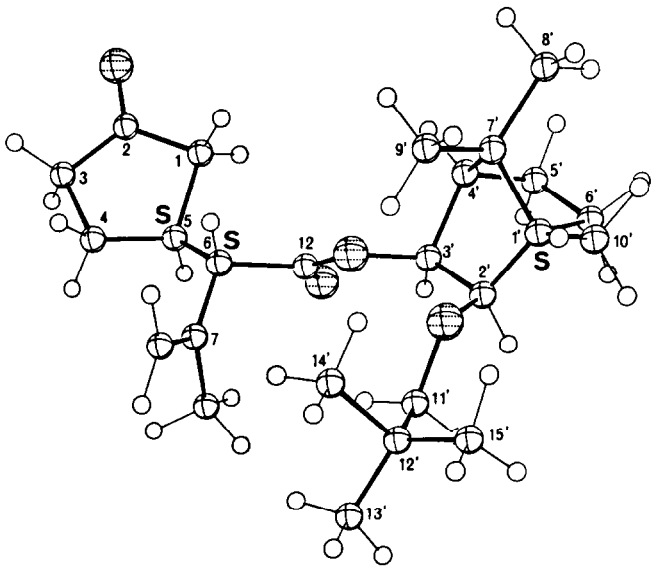


Si-Dienolate / Si-Enone Si-Dienolate / Re-Enone

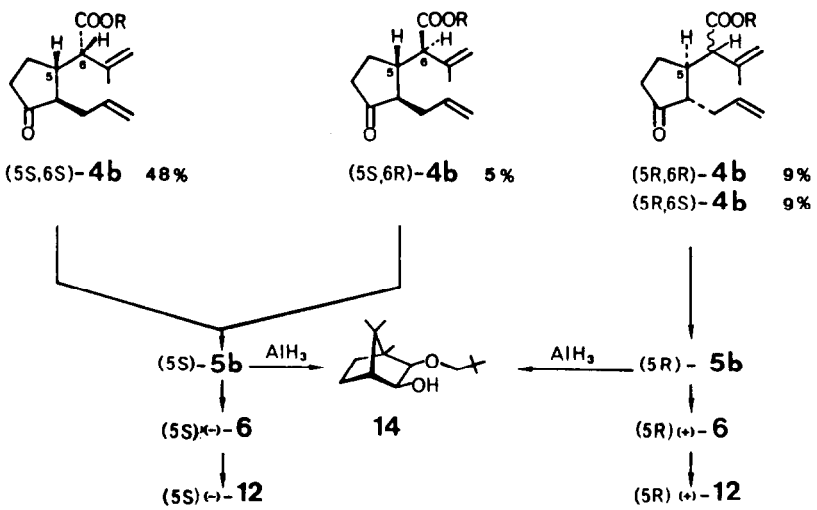
dienolate configuration becomes an issue. It was assumed to be (s-*cis*)-(E) based on differential nuclear Overhauser measurements of the ketene acetal obtained by successive treatment of methyl senecioate with LDA and TMSCl[6]. Thus, invoking a staggered approach of the trigonal centers and the operation of electronic factors transition states B and C (Scheme 2) were considered. Projection C exhibits steric repulsion between a cyclopentenone methylene and the dienolate methyl groups. Moreover, the carbonyl and the enolate oxygens are too far apart to permit chelation. On the other hand, orientation B is largely free of steric constraints and prone to chelation. It thus follows that the (5S,6S)-isomer 3b or 4b, formed *via* the more favorable transition state B should predominate[7].

Indeed the chiral senecioate 2b[8] gave on deprotonation with LDA in THF and subsequent addition of cyclopentenone (-78°, 5 min) a 63:21:9:7-mixture[9] of four diastereoisomers 3b (70% yield). X-ray-diffraction analysis of the major Michael adduct 3b[10] (Scheme 3) shows its (5S,6S)-chirality, in full agreement with the above arguments. Similar aprotic Michael addition of the dienolate derived from 2b to cyclopentenone and *in situ* trapping of the intermediate enolate with allyl bromide gave a 48:5:9:9 diastereoisomer mixture (GC) 4b (55%)[11] (Schemes 1 and 4)[3,12]. Thus, 48% asymmetric induction of the center C(5) has been achieved in the bifunctionalization 1 → 4b. This value was further confirmed by transformation of the crude reaction mixture to 13 which was analyzed by ^{19}F-NMR[13] and capillary-GC. The major isomer 4b (m.p. 28-30°), conveniently isolated in 37% yield by simple chromatography and crystallization, was assigned the (5S,6S)-configuration in view of the above X-ray evidence. This agrees with its conversion into enantiomerically pure (-)-khusimone (12). To this end ketalization and double bond-isomerization furnished the crystalline ester (5S)-5b, m.p. 86-87°. (5S,6R)-4b, non-separable from the more polar of the (5R)-4b-isomers, gave also (5S)-5b *via* the same sequence followed by chromatography. Reduction of (5S)-5b with AlH_3 refurnished the control element 14 and yielded the enantiomerically pure alcohol (5S)-6. The latter was further processed along the lines of the previous synthesis of (±)-12 (Schemes 1 and 4)[3,12]. Thus, in the magnesium-ene/carbonation step 8 → 9 → 10 center (5S) induced the (S)-configuration of center C(8) which in turn controlled the formation of (R)-C(1) during the final enolate alkylation. Consequently, optically pure (-)-khusimone, identified by comparison ($[\alpha]_D$, mixed m.p., capillary GC, IR, ^{1}H-NMR, ^{13}C-NMR, MS) with an authentic sample, was obtained in 14% overall yield

Scheme 3



Scheme 4



from cyclopentenone. Similarly, the minor (5R)-isomers 4b furnished non-natural (+)-khusimone.

We believe that this work, featuring an unusual double π-face-selective Michael process[14] is subject to further improvement; nevertheless it may provide useful insight and applicability in the area of asymmetric carbon,carbon bond formation.

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[9] The mixture 3b was analyzed by ^{1}H-NMR (360 MHz) integrating the C(3)-H doublets of the camphor-skeleton. The product ratio did not change on keeping the reaction mixture at -20° for 30 min.

[10] The major isomer 3b, m.p. 91-93°, was isolated by crystallization of its tosylhydrazone (EtOH, m.p. 145-147°), hydrazone cleavage with $TiCl_3$ *(B.P. Chandrasekhar, S.V. Sunthankar, S.G. Telang*, Chem. Ind. 1975, 87) and crystallization of the recovered 3b (aq. EtOH). The prisms are orthorhombic, a=10.395(2), b=10.647(3), c=23.058(3) A, V=2552 $Å^3$, space group $P2_12_12_1$, Z=4, D_X=1.053 g cm-3. Data were collected on a Philips PW 1100 diffractometer (Mo$K\alpha$-radiation). From 2056 measured reflections 1393 were significant. The structure was solved by a direct method (Multan-80-program) and refined by LS-methods to R=0.12. The hydrogen positions are calculated.

[11] Apart from the isomers 4b a bisallylated product (1.5%), 3b (5%) and a dienolate-γ-adduct (6%) were isolated by chromatography.

[12] The following optical rotations $[\alpha]_D^{22°}$ (c=g/100 ml $CHCl_3$) were measured: 2b, -31.6°(3.4); (5S, 6S)-4b, +43.6°(1.65); (5S)-5b, +7.6°(1.4); (5S)-6, -8.3°(2.53); (5S)-10, m.p. 129-130°, -3.3° (1.53); synth. (5S)-12, m.p. 80-82°, -126.7(0.98); nat. (5S)-12, -124.6°(1.0); (5R)-6, +7.7° (2.6); (5R)-10, +3.3(0.9); (5R)-12, +126.3°(1.0).

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