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Tandem Oxyallylations and Retro-ene Eliminations. One Pot Stereoselective Synthesis of Polypropionate Fragments with Three Contiguous Stereogenic Centers and One (E)-Alkene Unit.

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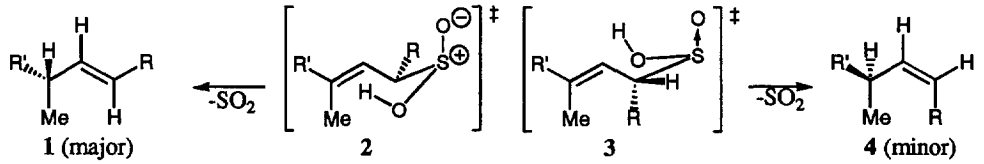
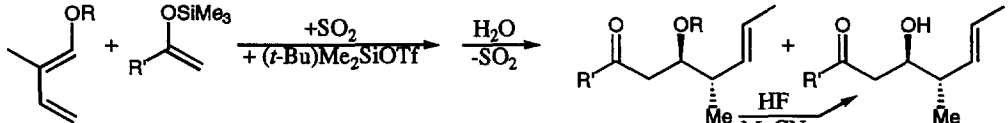
Abstract: Mixtures of (*E,E*)-2-methyl-1-silyloxypenta-1,3-dienes, enoxysilanes, SO_2 and (*t*-Bu)Me_2SiOTf (catalyst) generate (*Z*)-5-alkyl-1,3-dimethyl-6-oxo-4-silyloxyalk-2-enesulfinic acids that undergo stereoselective retro-ene eliminations of SO_2 with the formation of corresponding (*E*)-3-hydroxy-2-alkyl-4-methylalk-5-en-1-ones with 2,3-*syn* and 3,4-*anti* diastereoselectivity. © 1997 Elsevier Science Ltd.

In the presence of a Lewis acid the cycloadduct of (*E*)-1-methoxybutadiene to sulfur dioxide (a sultine or a sulfolene) probably undergoes heterolysis into a zwitterion that reacts with enoxysilanes to generate (*Z*)-6-oxo-4-methoxyalk-2-ene sulfinates.[2] These intermediates can be reacted with methyl iodide (S-alkylation) and afford the corresponding methyl sulfones, or they can be decomposed with SO_2 elimination via a retro-ene reaction that generates the corresponding 3-methoxyalk-5-en-1-ones.[2] The retro-ene elimination of SO_2 from 1-substituted alk-2-enesulfinic acids has been shown to be stereoselective, the chirality transfer from center C(1) to C(4) being assigned to preferred transition states adopting chair-like conformations with an optimal number of substituents residing in equatorial positions as shown here below with **2** → **1**.[3]



1 (major) **2** **3** **4** (minor)

In this report we demonstrate that high stereoselectivity can be expected for the chirality transfer during the retro-ene elimination of SO_2 from alk-2-enesulfinic acids derived from the oxyallylation[2] of enoxysilanes with the sulfur dioxide adducts of (*E,E*)-2-methyl-1-silyloxypenta-1,3-dienes. Furthermore, when the tandem oxyallylations and retro-ene eliminations start with enoxysilanes of diethyl ketone or 7-oxabicyclo[2.2.1]-heptan-2-ones, polypropionate chains[4] are generated with the stereoselective formation of three contiguous asymmetric centers and one (*E*)-olefinic moiety, in what is essentially a one pot operation.



5 **6** R' = Ph R = (*t*-Bu)Me_2Si **7** R' = Ph **8** R' = Ph
9 R' = Me **10** R' = Me **11** R' = Me

When a 1:2 mixture of diene **5** (R = (*t*-Bu)Me_2Si)[5] and enoxysilane **6** in CH_2Cl_2 was allowed to react with an excess of SO_2 in the presence of 0.1 mol. equiv. of (*t*-Bu)Me_2SiOTf at -78°C, the cycloadduct of SO_2

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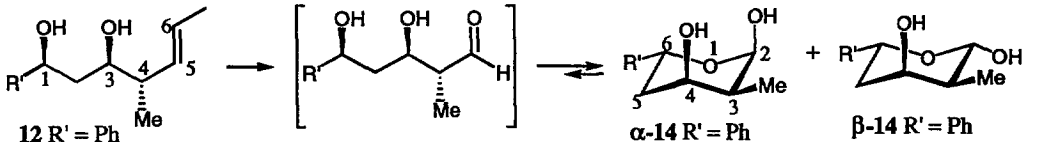
to **5** was formed in a few hours (as seen by ^{1}H-NMR at -78°C) giving a sultine (hetero-Diels-Alder addition[6]) or a sulfolene (cheletropic addition) with suprafacial selectivity (as confirmed by ^{1}H-NMR). This adduct reacted with (*t*-Bu)Me_2SiOTf and induced the oxyallylation of **6** to give an intermediate silyl sulfinate, that, upon addition of aqueous NH_4Cl/MeOH, was hydrolysed and decomposed (0-20°C, 20 h) into a 7:3 mixture of the protected and unprotected aldols **7** and **8**, respectively (95% yield, after flash chromatographic purification). Under similar conditions a 1:2 mixture of **5** and **9** led to a 2:1 mixture of aldols **10** and **11** (69% yield). The same reactions proceeded with similar yields when using (*E,E*)-2-methyl-1-tris(isopropyl)silyloxy-penta-1,3-diene (**5**, R = (*i*-Pr)$_3$Si)[5] instead of **5** (R = (*t*-Bu)Me_2Si). The *anti* relative configuration of the β and γ centers of the aldols was proven in the following way: reduction[7] (BEt_3/THF, -78°C, then $NaBH_4$) of **8** and **11** (also obtained by treatment of **7** and **10** with HF in MeCN, 20°C) afforded the corresponding *syn*-1,3-diols **12** (70%) and **13**[8] (86%), the ozonolyis of which (O_3/CH_2Cl_2, -78°C) with a Me_2S work-up (20°C, 2 h) gave the corresponding aldehydes that equilibrated with mixtures of α- and β-pyranoses **α-14/β-14** (45%) and **α-15/β-15** (66%), respectively. The vicinal proton/proton coupling constants[9] as well as the 400 MHz 2-D-NOESY ^{1}H-NMR spectra of these 4 compounds proved the *cis* relationship of their 3-methyl and 4-hydroxy substituents and thus the *anti* relative configuration of the γ-methyl aldols **7**, **8**, **10** and **11**.[10]

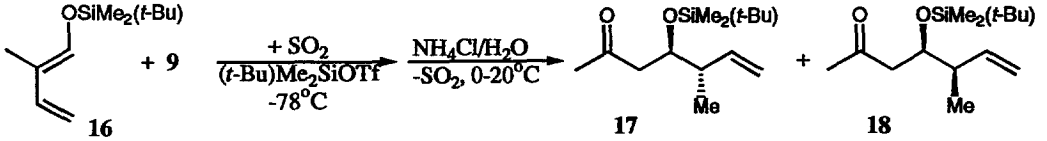


12 R' = Ph
13 R' = Me

α-14 R' = Ph
α-15 R' = Me

β-14 R' = Ph
β-15 R' = Me

When the tandem oxyallylation and retro-ene reaction sequence was carried out with the SO_2 cycloadduct of diene **16**[11] and enoxysilane **9** as above, a 1:1 mixture of **17** and **18** was obtained. This demonstrates[3] the necessity of the methyl group at the α-position of the intermediate alk-2-enesulfinic acid for a diastereoselective retro-ene elimination of SO_2.

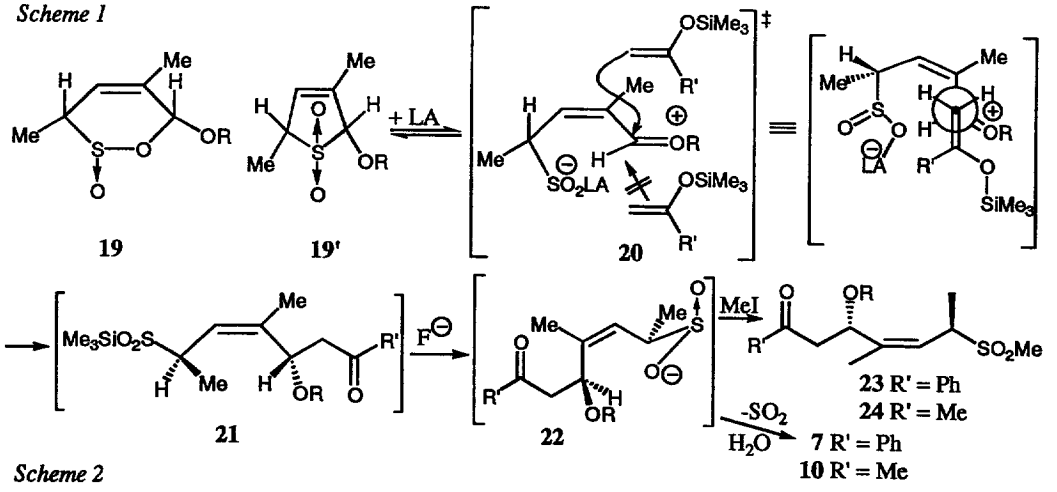


16 **17** **18**

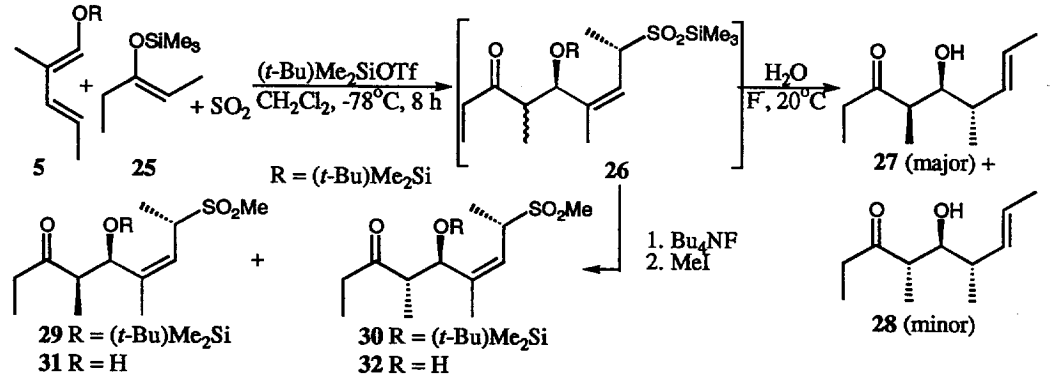
The high diastereoselectivity observed for reaction **5** + **6** + SO_2 → **7** + **8** + SO_2 and **5** + **9** + SO_2 → **10** + **11** + SO_2 can be interpreted in terms of the hypothetical mechanism shown in Scheme 1. The heterolysis of the cycloadducts **19** (or **19'**) induced by the Lewis acid must be highly diastereoselective and generate intermediates of type **20** that are quenched by the enoxysilanes on their less sterically hindered face, the face *anti* with respect to the sulfinyl moiety. This hypothesis is consistent with our observation that the alk-2-enesulfinate intermediates **22** (R' = Ph, Me) gave the sulfones **23** and **24** when reacted with MeI. Both reactions were highly diastereoselective.[12] For the reasons invoked above, the sulfinic acids **22** (R' = Ph, Me) undergo stereoselective retro-ene eliminations of SO_2 giving the observed aldols **7** and **10**.

The oxyallylations of (*E*)- and (*Z*)-enoxysilanes with the SO_2 cycloadduct of (*E*)-1-methoxybutadiene are *syn* selective.[2] This was also the case for the reaction of **25** with **19** (or **19'**) derived from **5** (Scheme 2) which generated a mixture of alk-2-enesulfinic acids **26** that were decomposed to a 7:3 mixture (70%) of the aldols **27** (*syn*, *anti*)[13] and **28** (*anti*, *anti*). When **26** was reacted with MeI (0-20°C) a 7:3 mixture of sulfones **29** and **30**, and a 7:3 mixture of the desilylated derivatives **31** and **32** were obtained in 83% total yield.[10,14]

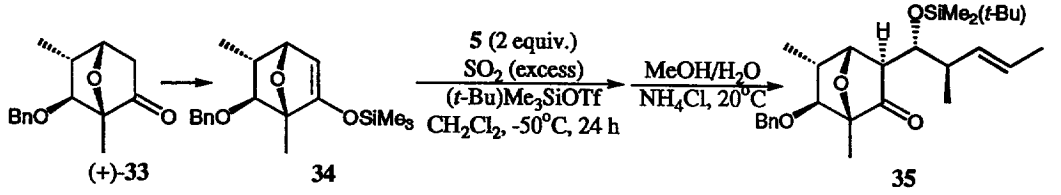
Scheme 1



Scheme 2



The tandem oxyallylation and retro-ene process applied to a 2:1 mixture of **5** and the enantiomerically pure enoxysilane **34** derived from (+)-**33**[15] in 97% yield (LDA/THF, -78°C, then Me_3SiCl, -78°C to 20°C) was highly *exo* face selective and furnished a single product **35** (72%).[10,16]



This work discloses a new method to prepare polypropionate fragments of the type (*E*)-3-hydroxy-2-alkyl-4-methylalk-5-en-1-one with 2,3-*syn* and 3,4-*anti* diastereoselectivity. The method provides a one pot procedure that creates three contiguous asymmetric carbon centers and one (*E*) olefinic moiety. Since (*E*,*E*)-2-methyl-1-silyloxypenta-1,3-dienes derive from two equivalents of propanal (via enolisation of 2-methylpent-2-enal), our tandem oxyallylation/retro-ene process can be viewed as a biomimetic approach.

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References and Notes

1. Current address: Dept. of Chemistry, University of Sherbrooke, Sherbrooke, P. Q. J1K 2R1, Canada.
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7. Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923-1930.
8. Data for **13**: oil, IR (film): 3570, 2965, 2880, 1510, 1460 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.54 (dqd, ^3J=15.3, 6.4, ^4J=1.0, HC(7)), 5.30 (ddq, ^3J=15.3, 8.4, ^4J=1.7, HC(6)), 4.03 (br. ddd, ^3J=9.7, 6.1, 2.1, HC(4)), 3.66 (br. s, OH), 3.58 (dqd, ^3J=10.5, 6.3, 2.1, HC(2)), 2.73 (s, OH), 2.12 (ddq, ^3J=8.4, 6.9, 6.1, HC(5)), 1.96 (dd, ^3J=6.4, ^4J=1.7, MeC(7)), 1.61 (ddd, ^2J=14.4, ^3J=2.1, 2.1), 1.43 (ddd, ^2J=14.4, ^3J=10.5, 9.7), 1.20 (dd, ^3J=6.3, MeC(1)), 0.99 (d, ^3J=6.9, MeC(5)).
9. Data of **α-14**: oil, ^{1}H-NMR (400 MHz, C_6D_6) δ_H: 7.98-7.26 (5H), 5.29 (dd, ^3J=12.0, 2.6, HC(6)), 5.08 (dd, ^3J=6.5, 2.9, HC(2)), 3.97 (d, ^3J=6.5, OH), 3.58 (dddd, ^3J=7.0, 3.5, 2.6, 2.6, HC(4)), 2.79 (d, ^3J=7.0, OH), 1.92 (ddd, ^2J=13.8, ^3J=3.5, 2.6, HC(5)), 1.57 (ddd, ^2J=13.8, ^3J=12.0, 2.6, H'C(5)), 1.53 (qdd, ^3J=7.0, 2.9, 2.6, HC(3)), 0.99 (d, ^3J=7.0, MeC(3)). Data for **β-14**: ^3J(HC(2),HC(3))=9.0, ^3J(HC(3), HC(4))=2.6 Hz. Data for **α-15**: oil, ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 4.96 (^3J=2.9, HC(2)), 4.35 (dqd, ^3J=11.7, 6.3, 2.5, HC(6)), 3.94 (ddd, ^3J=3.5, 2.7, 2.6, HC(4)), 1.85 (ddd, ^2J=13.7, ^3J=3.5, 2.5, HC(5)), 1.76 (ddq, ^3J=7.1, 2.9, 2.6, HC(3)), 1.52 (ddd, ^2J=13.7, ^3J=11.7, 2.7, HC(5)), 1.18 (d, ^3J=6.3, MeC(6)), 1.02 (d, ^3J=7.1, MeC(3)). Data for **β-15**: ^3J(HC(2),HC(3))=9.0, ^3J(HC(3),HC(4))=2.8, ^3J(HC(4), HC(5))=2.6, 3.1.
10. The structures of all the new compounds were confirmed with their spectral data and elemental analyses.
11. Derived from (E)-2,3-dimethylacrolein, b.p. 115°C ($16\cdot10^{-3}$ Torr).
12. The structures of methylsulfones **23** have not been established unambigously. This will be done in a future full paper.
13. Data for **26**: oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.49 (ddq, ^3J=15.4, 6.1), 5.40 (ddq, ^3J=15.4, 8.2, ^4J=1.2), 3.57 (ddd, ^3J=6.3, 3.6, 7.3), 2.69 (dq, ^3J=6.3, 7.1), 2.58 (d, ^3J=7.3, OH), 2.57 & 2.46 (2dq, ^2J=18.1, ^3J=7.2), 2.27 (ddq, ^3J=8.2, 6.9, 3.6), 1.67 (dd, 3H, ^3J=6.1, ^4J=1.2), 1.08 (d, 3H, ^3J=7.1), 1.06 (d, 3H, ^3J=6.9), 1.03 (t, 3H, ^3J=7.2).
14. The structures of these compounds were deduced from their spectral data and by derivatization as described.[2] The relative configuration of the methyl group at C(1) of **28-31** is tentative. It has not been established unambigously.
15. Sevin, A.-F.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 5920-5926.
16. Data for **34**: oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.37-7.27 (5H), 5.47 (dq, ^3J=15.6, 6.2), 5.37 (ddq, ^3J=15.6, 7.7, ^4J=1.3), 4.66 (d, ^3J=5.5), 4.56 & 4.52 (2d, ^2J=12.2), 3.89 (dd, ^3J=5.0, 2.7), 3.13 (d, ^3J=3.8), 2.45 (dm, ^3J=7.3), 2.26 (d, ^3J=5.0), 2.19 (dq, ^3J=2.7, 7.5), 1.66 (d, ^3J=6.2), 1.42 (s, 3H), 1.00 (d, 3H, ^3J=7.2), 1.00 (d, 3H, ^3J=7.5), 0.97 (s, 9H), 0.02 (s, 6H).

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