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Enantioselective synthesis of Bakuchiol using diazosulfonate C–H insertion to install the quaternary center

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ABSTRACT

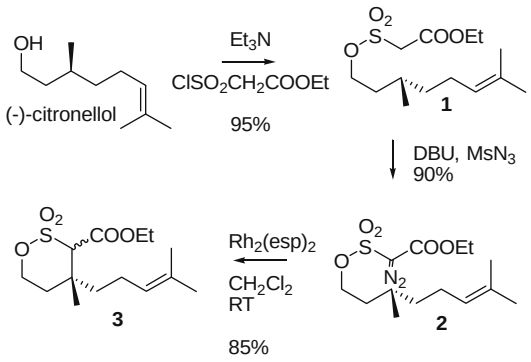
Bakuchiol was prepared from commercial (−)-citronellol using the diazosulfonate C–H insertion to control the regioselectivity and install the quaternary center.

We recently reported a modification of C–H insertion that permits assembly of six-membered sulfur-containing heterocycles,[1] effectively introducing substitution at a remote position to an existing functionality. The synthetic potential of this reaction has yet to be demonstrated. In this Letter we describe an application of this methodology for construction of the quaternary center in the structure of natural product Bakuchiol, which was isolated from seeds of *Psoralea corylifolia* L.,[2] and had a variety of applications. The two features of C–H insertion that make it particularly useful for this purpose are ease of insertion into a tertiary C–H bonds, and complete retention of configuration at the insertion site. Use of the sulfonate modification in this case appropriately controls the regioselectivity of insertion.

Thus, commercially available (−)-citronellol was converted to δ-sultone **3** using diazosulfonate C–H insertion in a manner identical to that previously reported by Du Bois (Scheme 1).[3] Our materials matched the reported compounds by spectral data.[12]

Initially, we attempted to reductively cleave the C–S bond in δ-sultone **3** using SmI_2/DMPU.[4] However, poor results were obtained. The expected reductive desulfonation product did appear to form, but in minor quantities, and contaminated by several byproducts (transformation of the double bond appeared to have taken place). Therefore, an alternative route was attempted (Scheme 2). DIBALH reduction of the ester in **3** to alcohol[13] proceeded cleanly. While it appeared to be possible to transform it to alcohol **6** by conversion to alkyl halide and treatment with zinc in DME, both of these reactions were riddled with difficulties. Reaction of alcohol **4** with Ph_3P/NBS or Ph_3P/I_2/ImH proceeded only at high temperatures (toluene, 90 °C), and in modest yields. Treatment with zinc tended to produce, along with **6,** elimination product **5** and other byproducts. This elimination product, **5**,[14] was easily available from **4** by mesylation and elimination, so we explored the possibility of its conversion to **6**.

Only a single example of reductive desulfonation of vinylic sulfonates appears to have been reported, using lithium in ammonia.[5] Under these conditions we saw formation of only small amounts (~5%) of the desired product. The major product, obtained as an apparent mixture of diastereomers, was not identified, but it appeared to retain the sulfonate moiety and lack the exomethylene double bond according to ^{1}H NMR spectrum. Several methods, reported for desulfonation of vinylic sulfones, also had limited success (decomposition was observed with $Na_2S_2O_4$,[6] low yields with BuMgCl–Ni(acac)$_2$ or BuMgCl–Pd(acac)$_2$,[7] no reaction with SmI_2 or SmI_2-DMPU, moderate yields with Na–EtOH–THF[8]). Eventually, we found that the procedure for desulfonation of vinylsulfones using Bu_3SnLi[9] was suitable in this case. Although it was somewhat touchy, this method would produce the desired alcohol **6**[15] in high yield, using two modifications to the reported procedure: (a) use of greater excess of the tin reagent (5 equiv or more) proved beneficial (b) use of TBAF (THF, reflux, 5 h) instead of silica gel for elimination of the tin adduct was more effective; also, nearly complete elimination was happening if the reaction mixture was warmed up to 0 °C before workup. Thus, effectively, a 'remote vinylation' of citronellol was achieved by this sequence. NMR study



Scheme 1. Preparation of δ-sultone from citronellol by C–H insertion.

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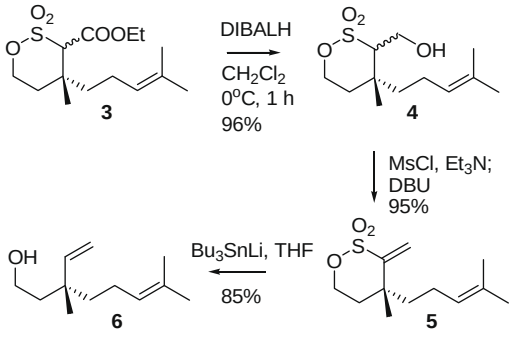
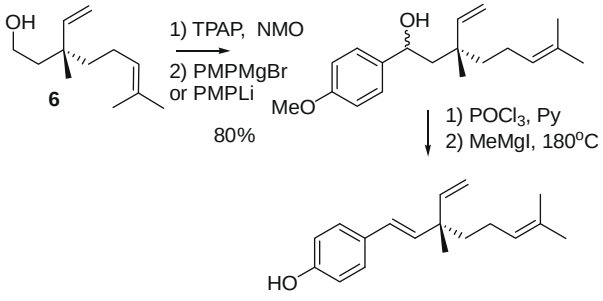


Scheme 2. Conversion of the sultone to the key intermediate.



Scheme 3. Preparation of Bakuchiol.

of *R*-acetylmandelic ester of alcohol **6** (and its independently prepared racemic form) confirmed that no detectable loss of optical purity took place.

The obtained alcohol was oxidized to the aldehyde,[16] and converted to Bakuchiol using the described method (Scheme 3),[10,11] via addition of *p*-methoxyphenyl magnesium bromide or lithium reagents (the latter was obtained by metal–halogen exchange between *p*-bromomethoxybenzene and *n*-butyllithium), elimination and demethylation. The synthetic compound matched the natural product by spectral data and specific rotation.

Thus, synthesis of Bakuchiol was achieved using diazosulfonate C–H insertion to install the quaternary center, demonstrating the utility of this methodology. Further studies on synthetic applications of this modification of C–H insertion are being performed and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.147.

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12. Specific rotations for optically pure compounds: Ethyl (3*S*),2-[[(3,7-dimethyl-6-octen-1-yl)oxy]sulfonyl]-acetate (**1**): $[\alpha]_D^{20} = -2.0$ (1.2, $CHCl_3$).Ethyl (3*S*)-2-diazo-2-[[(3,7-dimethyl-6-octen-1-yl)oxy]sulfonyl]-acetate (**2**): $[\alpha]_D^{20} = -35.6$ −44.6 (1.2, $CHCl_3$). Constant rapid oscillation in the specified range was observed for undetermined reasons.(4*R*)-3-Carbethoxy-4-methyl-4-(4-methylpent-3-enyl)-1,2-oxathiane-2,2-dioxide (**3**): Less polar isomer: $[\alpha]_D^{20} = +48.3$ (1.1, $CHCl_3$). More polar isomer: $[\alpha]_D^{20} = -52.7$ (1.2, $CHCl_3$).
13. Physical data for (4*R*)-3-hydroxymethyl-4-methyl-4-(4-methylpent-3-enyl)-1,2-oxathiane-2,2-dioxide (**4**).Less polar isomer: colorless oil. R_f 0.44 (1:2 EtOAc/hexanes). $[\alpha]_D^{20} = -11.6$ (1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (t, *J* = 7 Hz, 1H), 4.66 (td, *J* = 11.5, 2.5 Hz, 1H), 4.50 (dt, *J* = 11.5, 4 Hz, 1H), 4.16–4.22 (m, 1H), 4.01–4.07 (m, 1H), 3.21 (dd, *J* = 8, 3 Hz, 1H), 2.34 (dd, *J* = 9.5, 4.5 Hz, 1H), 1.95–2.05 (m, 3H), 1.70 (s, 3H), 1.63–1.69 (m, 2H), 1.62 (s, 3H), 1.44–1.52 (m, 1H), 1.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 133.0 (C), 123.1 (CH), 69.5 (CH2), 68.0 (CH), 58.2 (CH2), 41.3 (CH2), 38.4 (C), 35.8 (CH2), 25.9 (CH3), 22.0 (CH2), 20.5 (CH3), 17.9 (CH3). HRMS (ESI) calcd for $C_{12}H_{26}NO_4S$ [M+NH_4] 280.1583, found 280.1583. IR (neat, cm^{-1}): 3527, 2971, 2919, 1461, 1348, 1172.More polar isomer: colorless oil. R_f 0.38 (1:2 EtOAc/hexanes). $[\alpha]_D^{20} = +23.4$ (0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.07 (t, *J* = 7 Hz, 1H), 4.55 (t, *J* = 5.5 Hz, 2H), 4.14–4.21 (m, 1H), 4.02–4.07 (m, 1H), 3.11 (dd, *J* = 8, 2,5 Hz, 1H), 2.52 (dd, *J* = 10, 4 Hz, 1H), 1.84–1.96 (m, 4H), 1.69 (s, 3H), 1.62–1.66 (m, 1H), 1.61 (s, 3H), 1.34–1.40 (m, 1H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.8 (C), 123.3 (CH), 70.3 (CH), 69.5 (CH2), 58.5 (CH2), 38.7 (C), 35.7 (CH2), 34.8 (CH2), 25.9 (CH3), 25.6 (CH3), 21.9 (CH2), 17.9 (CH3). HRMS (ESI) calcd for $C_{12}H_{26}NO_4S$ [M+NH_4] 280.1583, found 280.1584. IR (neat, cm^{-1}): 3527, 2970, 2924, 1459, 1344, 1172.
14. Physical data for 3-methylene-4-methyl-4-(4-methylpent-3-enyl)-1,2-oxathiane-2,2-dioxide (**5**): Colorless oil. R_f 0.49 (1:5 EtOAc/hexanes). $[\alpha]_D^{20} = -52.7$ (0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (s, 1H), 5.68 (s, 1H), 5.11 (t, *J* = 7 Hz, 1H), 4.79 (td, *J* = 11.5, 2.5 Hz, 1H), 4.45 (dt, *J* = 11.5, 4 Hz, 1H), 2.12–2.18 (m, 1H), 2.00 (ddd, *J* = 15.5, 11, 4.5 Hz, 1H), 1.89–1.95 (m, 2H), 1.73 (ddd, *J* = 14, 4, 2.5 Hz, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.38–1.45 (m, 1H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.5 (C), 132.6 (C), 123.5 (CH), 121.4 (CH2), 68.8 (CH2), 41.8 (C), 39.0 (CH2), 37.5 (CH2), 25.9 (CH3), 23.1 (CH2), 17.8 (CH3). ^{13}C NMR (C_6D_6, 125 MHz): δ 151.1 (C), 132.4 (C), 124.5 (CH), 121.0 (CH2), 68.4 (CH2), 41.7 (C), 39.2 (CH2), 37.8 (CH2), 26.2 (CH3), 25.7 (CH3), 23.7 (CH2), 18.0 (CH3). HRMS (ESI) calcd for $C_{12}H_{24}NO_3S$ [M+NH_4]$^+$ 262.1477, found 262.1490. IR (neat, cm^{-1}): 2970, 2918, 2857 1456, 1353, 1185. There is 1 less signal in ^{13}C spectrum of the compound due to accidental equivalence of chemical shifts of two methyl signals. It is consistent with the increased height of the signal and confirmed by a ^{13}C spectrum in C_6D_6, where these two carbons show separately.
15. Although alcohol **6** was previously reported in the literature (in racemic form), no complete set of physical data was provided. Data for (*R*)-3,7-dimethyl-3-vinyloct-6-en-1-ol (**6**):Colorless oil. R_f 0.42 (1:5 EtOAc/hexanes). $[\alpha]_D^{20} = -20.6$ (0.35, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.09 (t, *J* = 7 Hz, 1H), 5.04 (dd, *J* = 10.5, 1 Hz, 1H), 4.96 (dd, *J* = 17.5, 1 Hz, 1H), 3.62–3.70 (m, 2H), 1.86–1.94 (m, 2H), 1.57–1.70 (m, 8H), 1.68 (s), 1.59 (s), 1.42 (br s, 1H), 1.32 (dd, *J* = 9.5, 8 Hz, 2H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.2 (CH), 131.5 (C), 124.9 (CH), 112.3 (CH2), 60.1 (CH2), 43.6 (CH2), 41.7 (CH2), 38.9 (C), 25.9 (CH3), 22.8 (CH2), 22.6 (CH3), 17.8 (CH3). HRMS (ESI) calcd for $C_{12}H_{26}NO$ [M+NH_4]$^+$ 200.2014, found 200.2018. IR (neat, cm^{-1}): 3337, 3082, 2967, 2926, 1636 1453, 1376, 1048.
16. (*R*)-3,7-Dimethyl-3-vinyloct-6-enal: $[\alpha]_D^{20} = -25.0$ (0.5, $CHCl_3$).