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A concise synthesis of (+)-cassiol

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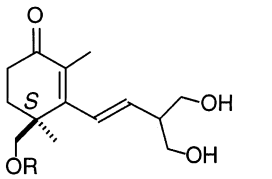
Abstract—A synthesis of the anti-ulcerogenic compound (+)-cassiol **1b** with 43% overall yield has been achieved. This short and efficient synthesis features the one-pot Julia olefination reaction of lactol (*S*)-**2** with sulfone **3b** through the key intermediate (−)-**4b**.

During the course of a pharmacological analysis of the aqueous extract of the dried stem bark of *Cinnamomum cassia* Blume, Fukaya et al.[1] isolated the serotonin-induced anti-ulcerogenic glucoside, cassioside **1a**, whose enzymatic hydrolysis afforded the aglycone (+)-cassiol **1b**, exhibiting a more potent anti-ulcer activity than cassioside itself.

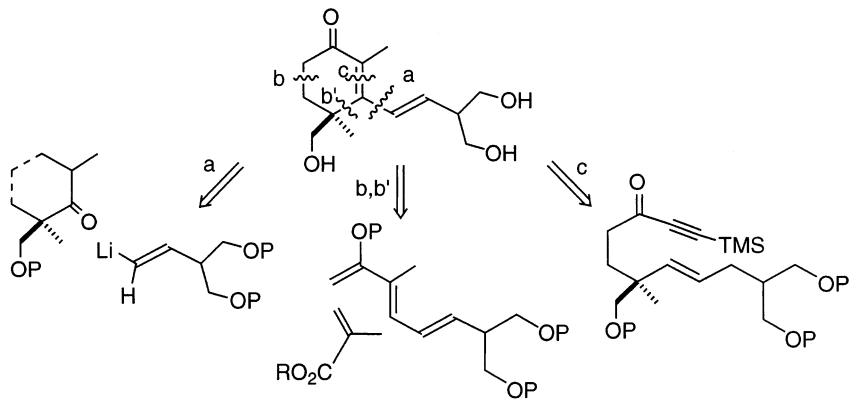
The structural features and pharmacological activity of cassiol have prompted extensive synthetic efforts, which have culminated in several syntheses of **1b** over the past decade.



1a : R=β-D-glucopyranosyl
1b : R=H

As depicted retrosynthetically in Scheme 1, three main strategies were used for the synthesis of (+)-cassiol. The one involving disconnection **a**, based on the assembly of a chiral and adequately functionalized cyclohexenone/cyclohexanone intermediate, and its coupling with a side-chain precursor, was used by several research groups.[2–8] Disconnection **bb′** involves a chiral Diels–Alder cycloaddition reaction[9,10] and disconnection **c**, a cycloisomerization in an ene type fashion.[11] A comparative analysis of these approaches indicates that the sequence in which the key step is a catalyzed enantioselective Diels–Alder reaction[9] is, by far, the most efficient with respect to the number of synthetic steps and the overall yield (40%).

We have recently developed a rather simple sequence for the preparation of both enantiomers of lactol **2**[12] which, as a racemic mixture, had been used by White et al. for the synthesis of (±) trisporic acids.[13] The



Scheme 1.

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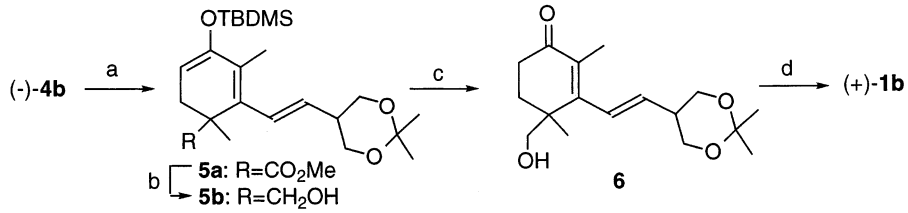


Scheme 2. *Reagents and conditions*: (a) TBDMSOTf, Et_3N, Cl_2CH_2, 0°C, then rt, 1 h; (b) DIBAL-H, THF, −78°C, 1 h; (c) TBAF, THF, rt, 1 h; (d) 6N HCl, MeOH, rt, 1.5 h.

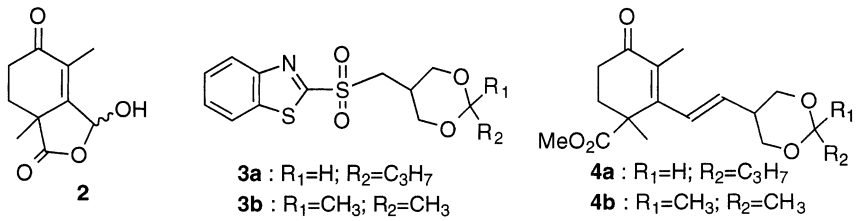
availability of this key intermediate prompted us to study a convergent approach for the synthesis of (+)-cassiol **1b**, via an olefination sequence which has not previously been explored.

Our first choice for the synthesis of **1b** was to use a simple Wittig reaction however, due to the difficulties found in the preparation of the appropriate phosphonium bromide, we decided to apply the one-pot olefination reaction recently reported by Julia et al.[14] and successfully used by Kociensky et al. in the synthesis of several natural products.[15,16]

We found that by the addition of lactol (±)-**2** to the anion of the benzothiazolylsulfone **3a** generated with LDA in THF at −80°C, the desired product **4a** was obtained in only 18% yield after treatment of the crude product with excess diazomethane and purification by column chromatography.

ing the sequence used for racemic cassiol, (+)-**1b** was obtained in 43% overall yield. The sequence with optically active compounds was carried out without isolation and purification of the intermediates **5a**, **5b** and **6**, requiring only chromatographic purification of (−)-**4b**[22] and of (+)-**1b**.[23]

The synthesis of (+)-**1b** described in this report, featuring an excellent approach for the olefination of lactols, is short and efficient and uses simple reactions that allow good reproducibility and material throughput. Although the anti-ulcerogenic activity of **1b** is probably due to the presence of a cyclohexenone moiety in the molecule,[24] the availability of (*R*)-**2** and the easy preparation of different benzothiazolylsulfones will allow the synthesis of (−)-**1b** and its analogs in order to elucidate the effect of the configuration at C(4) and the side chain on the pharmacological activity.



Careful analysis of the reaction mixture allowed us to identify the methyl ester of unchanged starting material, together with products that suggest that **2** undergoes an unwanted Cannizzaro-type reaction under these conditions.[17] However, if a solution of (±)-**2** in THF was first treated with equimolar sodium hydride and then added to the anion of the benzothiazolylsulfones **3a** or **3b**,[18] the coupling products **4a** and **4b** are, respectively obtained in ca. 75% yields, without formation of the side products.[19,20]

With the coupling products **4a** and **4b** in hand, we analyzed several approaches to (±)-**1b**, including its reduction to a mixture of diastereomeric diols, selective protection of the primary alcohol followed by oxidation of the allylic alcohol or selective oxidation of the allylic alcohol and adjustment of the diol protecting group, finally we found that formation of the silyl enol ether **5a**,[21] from **4b**, followed by reduction with DIBAL-H to **5b**[21] and deprotection through **6**,[21] gave (±)-**1b** in good overall yield (Scheme 2). Starting with (*S*)-**2** and follow-

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18. Compound **3b**: mp 112.8–113.3°C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.24–8.20 (1H, m), 8.10–8.00 (1H, m), 7.66–7.60 (2H, m), 4.12 (2H, dd, A part of ABX, $J=12.0$ and 3.5 Hz), 3.81 (2H, dd, B part of ABX, $J=12.0$ and 4.6 Hz), 3.76 (2H, d, $J=6.10$ Hz), 2.41 (1H, m), 1.43 (3H, s), 1.39 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.68 (s), 152.40 (s), 136.49 (s), 127.98 (d), 127.57 (d), 125.27 (d), 122.20 (d), 98.25 (s), 63.09 (t, two carbons), 54.30 (t), 29.45 (d), 25.57 (q), 21.56 (q). Anal. calcd for $C_{14}H_{17}NO_4S_2$: C, 51.36; H, 5.23; N, 4.28; S, 19.58. Found: C, 51.16; H, 5.23; N, 4.35; S, 19.56%.
19. We thank Professor S. V. Ley (Cambridge) for this helpful suggestion.
20. By treatment of **2** with sodium hydride in THF solution at room temperature the corresponding anion is readily formed. We believe that under these conditions an equilibrium between the alkoxide and its open form is established, allowing in this way fast attack of the lithiated benzothiazolylsulfone to the carbonyl of the free aldehyde group, leading to the coupling product. Furthermore, since the attack of any nucleophilic base present in the reaction medium to the neutral lactol cannot occur under these conditions, the formation of Cannizaro-type side products is avoided.
21. Compounds (±)-**5a**, (±)-**5b** and (±)-**6** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy. The data of (±)-**6** are identical with those reported in the literature for (−)-**6**.[9]
22. Compound (−)-**4b**: colorless oil; $[\alpha]_D^{27}=-25.3$ (c 3, $CHCl_3$), e.e. = 97%, the enantiomeric purity was established by ^{1}H NMR analysis employing the shift reagent *tris*(3-[heptafluoropropyl-hydroxymethylene]-*d*-camphorato)europium(III) derivative [Eu(hfc)$_3$]; IR (neat) 1728, 1664, 1634, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.27 (1H, d, $J=16.4$), 5.67 (1H, dd, $J=16.4$ and 8.2 Hz), 3.95–3.85 (2H, m), 3.80–3.60 (2H, m), 3.68 (3H, s), 2.60–2.30 (4H, m), 1.95 (1H, m), 1.87 (3H, s), 1.47 (3H, s), 1.43 (3H, s), 1.42 (3H, s). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.78 (s), 175.85 (s), 151.69 (s), 133.92 (d), 132.41 (s), 128.86 (d), 97.62 (s), 63.66 (t, two carbons), 52.22 (q), 46.78 (s), 39.33 (d), 34.05 (t), 33.39 (t), 26.59 (q), 22.66 (q), 20.92 (q), 12.39 (q). HRMS calcd for $C_{18}H_{26}O_5$ (M^+): 322.1780, found: 322.1784.
23. Compound (+)-**1b**: colorless oil, $[\alpha]_D^{30}=+8.3$ (c 0.35, MeOH); IR (neat) 3368, 2930, 2876, 1644, 1594, 1456, 1044 cm^{-1}; ^{1}H NMR (D_2O, 200 MHz): δ 6.28 (1H, d, $J=16.3$ Hz), 5.67 (1H, dd, $J=16.3$ and 8.4 Hz), 3.76 (1H, d, $J=11.4$ Hz), 3.75 (2H, dd, A part of ABX, $J=11.5$ and 5.9 Hz), 3.66 (2H, dd, B part of ABX, $J=11.1$ and 7.0 Hz), 3.43 (1H, d, $J=11.5$ Hz), 2.71–2.55 (3H, m), 2.17 (1H, ddd, $J=13.4$, 9.8 and 6.0 Hz), 1.81 (3H, d, $J=0.9$ Hz), 1.74 (1H, ddd, $J=13.6$, 6.1 and 6.1 Hz), 1.12 (3H, s). The signals at δ 3.75 and 3.66 simplify into an AB quartet upon irradiation at δ 2.67. This ^{1}H NMR spectrum is coincident with that reported by Fukaya et al. for (+)-**1b** at 250 MHz.[1] ^{1}H NMR (D_2O, 500 MHz): δ 6.28 (1H, dt, $J=16.3$ and 1.0 Hz), 5.67 (1H, dd, $J=16.2$ and 8.4 Hz), 3.76 (1H, d, $J=11.4$ Hz), 3.745 (1H, dd, $J=11.2$ and 5.9 Hz), 3.740 (1H, dd, $J=11.2$ and 5.9 Hz), 3.670 (1H, dd, $J=11.2$ and 7.1 Hz), 3.666 (1H, dd, $J=11.2$ and 7.1 Hz), 3.43 (1H, d, $J=11.4$ Hz), 2.68–2.52 (3H, m), 2.17 (1H, ddd, $J=13.5$, 10.4 and 5.3 Hz), 1.81 (3H, d, $J=0.9$ Hz), 1.75 (1H, ddd, $J=13.5$, 6.6 and 5.8 Hz), 1.12 (3H, s). This ^{1}H NMR spectrum is essentially identical with that reported by Corey et al. for synthetic (+)-**1b** at 500 MHz.[9] ^{13}C NMR (D_2O, 50 MHz): δ 207.12 (s), 164.87 (s), 139.17 (d), 134.35 (s), 131.37 (d), 70.44 (t), 64.55 (t, two carbons), 50.30 (d), 43.18 (s), 35.89 (t), 33.28 (t), 23.02 (q), 15.63 (q). These data are consistent with those reported by Corey et al. for (+)-**1b** at 100 MHz.[9]
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