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A convergent approach for the total synthesis of (−)-synrotolide diacetate

P. Srihari,* B. Prem Kumar, K. Subbarayudu and J. S. Yadav

Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A simple carbohydrate based convergent approach towards the total synthesis of (−)-synrotolide diacetate is described employing a Sharpless asymmetric epoxidation, a Grignard assisted lactol opening with a terminal alkyne and a Wittig reaction using the Horner–Emmons reagent as the key steps.

Several natural products possessing α,β-unsaturated lactone rings display major pharmacologically relevant properties.[1] Recently, lactones such as anamarine **1**,[2] hyptolide **2**,[3] spicigerolide **3**,[4] synargentolide **4**[5] and synrotolide **5**[6] were isolated from species of *Hyptis*, *Syncolostemon* and related genera of the family Lamiaceae (Fig. 1). These compounds contain a polyoxygenated chain connected to an unsaturated δ-lactone ring and were found to display excellent cytotoxicity against human tumor cells, as well as antifungal and antimicrobial activity.[7] These excellent bioactivities have encouraged us to take up the synthesis of synrotolide and its diacetate derivative. So far, and to the best of our knowledge, there is only one report on the synthesis of a derivative of this natural product.[8]

In continuation of our research on the synthesis of lactone-containing natural products,[9] we herein disclose our strategy towards the synthesis of synrotolide and its diacetate derivative following a convergent approach utilizing Sharpless asymmetric epoxidation, a Grignard assisted lactol opening with a terminal alkyne and a stereoselective Wittig reaction using the Horner–Emmons reagent, as key steps. Retrosynthetic analysis of synrotolide **5** revealed an intermediate **6**, which can be synthesized via a convergent approach utilizing two key

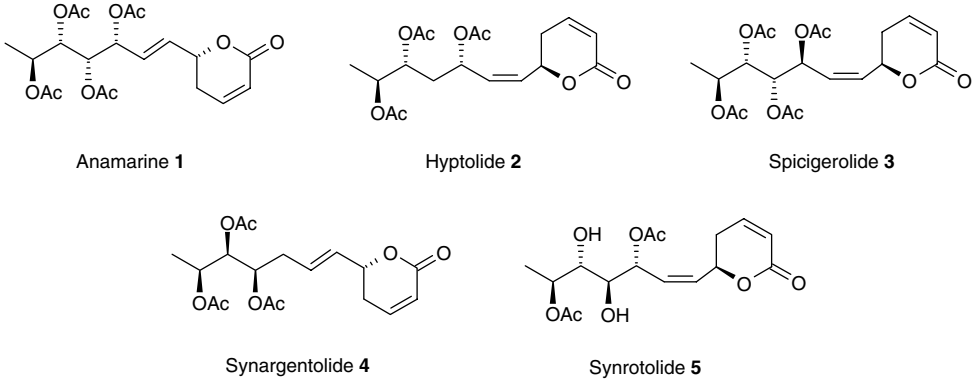

Figure 1.

* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: srihari@iict.res.in

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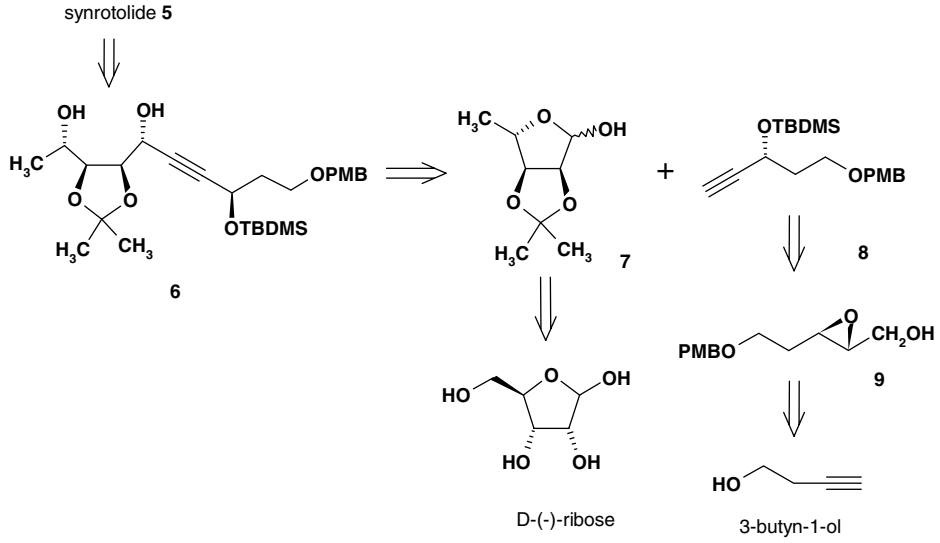
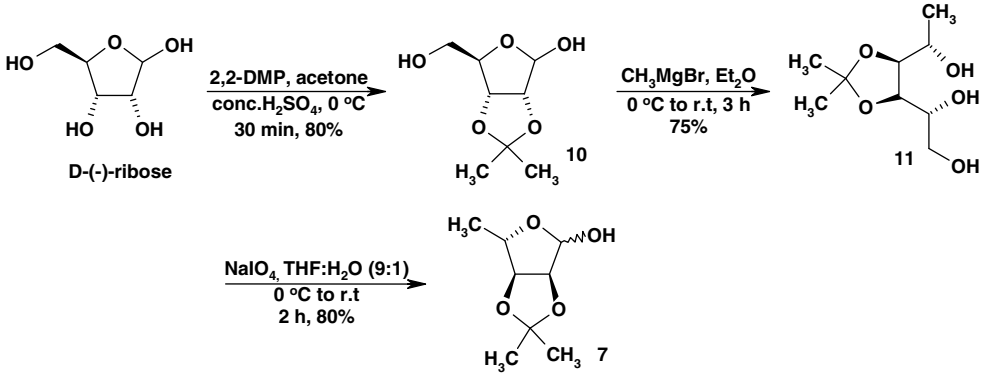
fragments **7** and **8**. These two fragments in turn could be obtained from readily available D-(−)-ribose and 3-butyn-1-ol (Scheme 1).

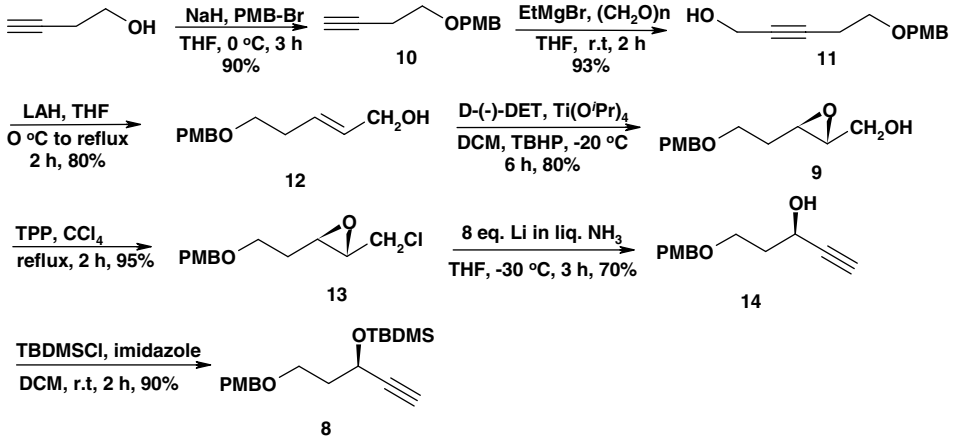
The key fragment **7** was synthesized from readily available D-(−)-ribose, by isopropylination with acetone, 2,2-dimethoxypropane and concd H_2SO_4 to give **10**.[10]



Scheme 1.



Scheme 2.

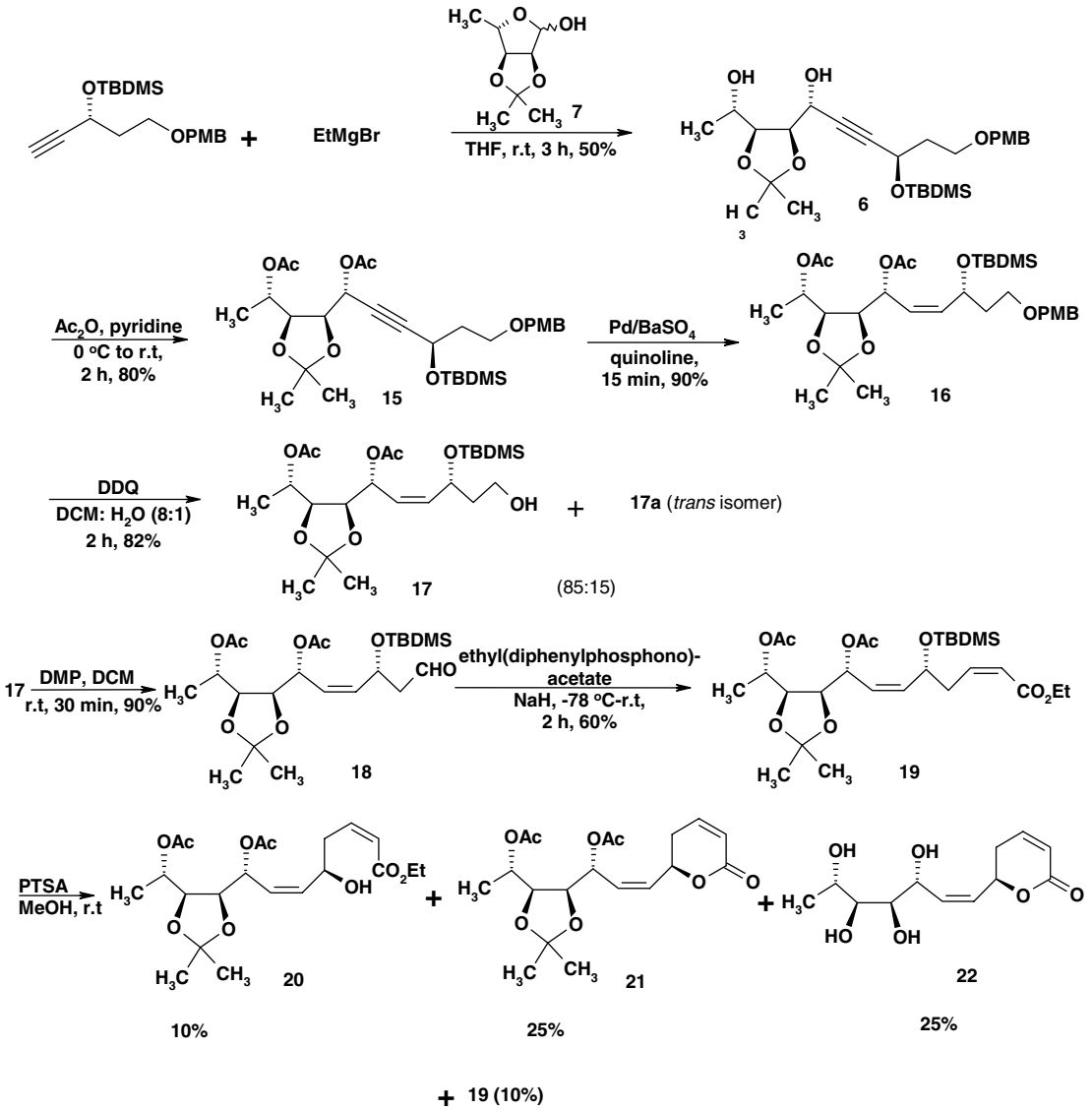


Scheme 3.

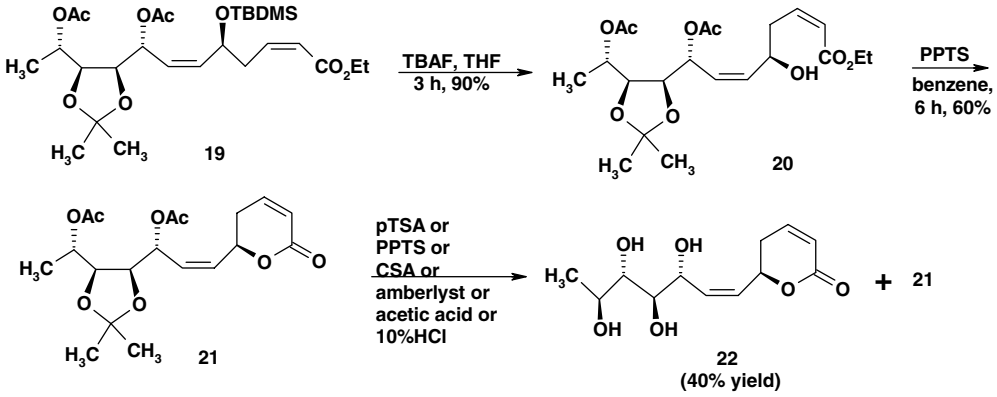
Compound **10** on Grignard reaction with excess methylmagnesium iodide gave triol **11** exclusively,[11] which on oxidative cleavage with $NaIO_4$ yielded lactol **7** (Scheme 2) in 80% yield.

The other key intermediate **8** was synthesized starting from 3-butyn-1-ol. Accordingly, the alcohol was protected as the *para*-methoxybenzyl ether **10** with NaH and *para*-methoxybenzyl bromide. Next, the free acetylene was treated with EtMgBr to generate the carbanion and was quenched with paraformaldehyde to afford propargyl alcohol **11**. Alcohol **11** was reduced with $LiAlH_4$ in THF to give allyl alcohol **12**, Sharpless epoxidation[12] of which with D-(−)-DET and TBHP afforded the epoxy alcohol **9**. The primary alcohol was converted to chloride **13** with triphenylphosphine and CCl_4 under reflux and then treated with excess lithium in liq. ammonia to give acetylenic alcohol **14** as reported earlier by our group for the preparation of chiral propargyl alcohols.[13] The alcohol was protected with TBDMSCl and imidazole to afford *tert*-butyldimethylsilyl ether **8** (Scheme 3).

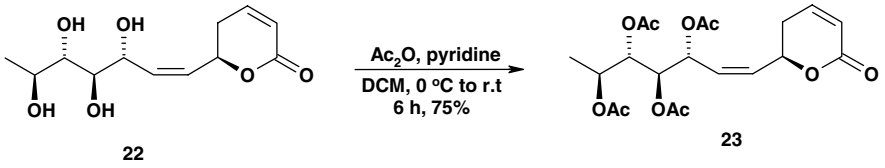
With the two intermediates **7** and **8** in hand, we proceeded to couple the in situ metalated acetylene (obtained by treating **8** with ethyl magnesium bromide) with lactol **7** to afford the functionalized intermediate **6**.[14] Diol **6** was protected as diacetate **15** with acetic anhydride and then the triple bond was partially reduced to the cis olefin **16** using Lindlar's catalyst.[15] PMB deprotection was achieved using DDQ to give compound **17**. However, we observed 10–15% isomerization of **17** to **17a** (trans isomer) during this reaction, and the isomers were easily separable by column chromatography. Alcohol **17**, on oxidation with Dess Martin periodinane in DCM, afforded aldehyde **18** which was subjected to a Wittig reaction with ethyl(diphenylphosphono)acetate[16] to yield the *Z*-unsaturated ester **19**, exclusively. At this stage, the stereochemistry of compound **19**, particularly at C8–C9, was determined by



Scheme 4.



Scheme 5.



Scheme 6.

studying NOSEY and COSY spectra. Also the coupling constant values confirmed the geometry of the product. We envisioned that PTSA could be used to obtain (−)-synrotolide from **19** in a one-pot reaction via a three-step sequence (TBDMS deprotection, lactonization and acetonide deprotection) (Scheme 4). However, this reaction was time sensitive and always resulted in either the TBDMS deprotected alcohol **20** or lactone **21** with the acetonide moiety intact or lactone tetrol **22** but with no yield of the expected synrotolide **5**.

A prolonged reaction time increased the yield of **22** with a simultaneous decrease in the yields of **20** and **21** but without any success in the formation of **5**. Other acids such as PPTS, CSA, amberlyst and acetic acid also gave mixtures of **20**, **21** and **22**. Alternatively, compound **19**, on treatment with TBAF afforded **20** in 90% yield, which was subjected to cyclization with PPTS in benzene to afford lactone **21**. Attempts to deprotect the acetonide group with PTSA, PPTS, CSA, amberlyst, acetic acid, 10% HCl, $CuCl_2{\cdot}2H_2O$ and $FeCl_3$ resulted in either recovery of starting material, formation of tetrol **22** or decomposition of the starting material after prolonged reaction times (Scheme 5).

After several unsuccessful attempts to obtain the natural product (−)-synrotolide from **21**, we decided to synthesize the diacetate derivative **23**, of synrotolide. Thus, tetrol **22** was protected as its tetraacetate **23** using acetic anhydride in pyridine. The spectral properties were found to be similar to those reported earlier (Scheme 6).[8,17,18]

In conclusion, a carbohydrate based convergent method for the synthesis of (−)-synrotolide diacetate has been described. The application of this strategy for the total synthesis of the natural product, (−)-synrotolide is under investigation.

Acknowledgements

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18. *Spectroscopic data of* **19**: Colorless liquid; IR (neat) 3426, 2986, 2932, 2857, 1742, 1645, 1465, 1372, 1174, 1058, 941, 836, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.28–6.43 (m, 1H), 5.81 (dt, 1H, $J = 1.5$, 11.7 Hz), 5.49–5.71 (m, 2H), 5.22–5.35 (m, 1H), 4.94 (p, 1H, $J = 6.2$ Hz), 4.66–4.79 (m, 1H), 4.04–4.23 (m, 4H), 2.73–3.03 (m, 2H), 2.04 (s, 3H), 2.00 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.23 (t, 3H, $J = 7.4$ Hz), 1.26 (d, 3H, $J = 6.2$ Hz), 0.85 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.34, 169.67, 166.33, 146.38, 139.57, 123.82, 121.21, 108.88, 78.43, 77.69, 69.08, 68.17, 67.60, 59.86, 38.12, 27.06, 25.94, 25.32, 21.55, 21.07, 18.19, 16.94, 14.45, −4.38, −4.99. LCMS: m/z 542 (M^+). $[\alpha]_D^{20}$ +14.0 (c 0.04 $CHCl_3$). HRMS for $C_{27}H_{46}O_9NaSi$: Calcd 565.2815; found, 565.2808. Compound **22**: white solid; mp 175–177 °C. ^1H NMR (200 MHz, DMSO-d_6): δ 7.01–7.16 (m, 1H), 5.99 (d, 1H, $J = 10.6$ Hz), 5.58–5.78 (m, 2H), 5.23–5.43 (m, 1H), 5.01 (d, 1H, $J = 4.8$ Hz), 4.87 (d, 1H, $J = 4.8$ Hz), 4.42–4.58 (m, 3H), 3.75–3.92 (m, 1H), 3.09–3.22 (m, 1H), 2.34–2.58 (m, 3H), 1.04 (d, 3H, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.57, 147.16, 133.70, 127.75, 120.13, 74.78, 74.72, 73.93, 67.78, 67.24, 29.16, 17.10. $[\alpha]_D^{20}$ −26.0 (c 0.5 MeOH). LCMS: m/z 257 (M^+H). HRMS for $C_{12}H_{17}O_6$: Calcd 257.1033; found, 257.1025. Compound **23**: colorless solid, mp 98–100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.89 (ddd, 1H, $J = 9.7$, 5.3, 3.0 Hz), 6.03–6.10 (m, 1H), 5.77–5.89 (m, 2H), 5.41–5.46 (m, 1H), 5.30 (dd, 1H, $J = 7.9$, 3.5 Hz), 5.21 (ddd, 1H, $J = 7.7$, 3.4, 1.3 Hz), 4.89–5.06 (m, 2H), 2.34–2.55 (m, 2H), 2.17 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.22 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.00, 169.93, 169.90, 169.88, 163.66, 144.67, 132.85, 126.34, 121.79, 72.26, 72.14, 71.11, 71.06, 71.02, 68.87, 29.58, 21.28, 21.15, 21.07, 14.35. $[\alpha]_D^{20}$ −10.7 (c 0.05 $CHCl_3$). LCMS: m/z 426 (M^+). HRMS for $C_{20}H_{26}O_{10}Na$: Calcd 449.1421; found, 449.1423.