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# Stereoselective synthesis of (+)-hyptolide

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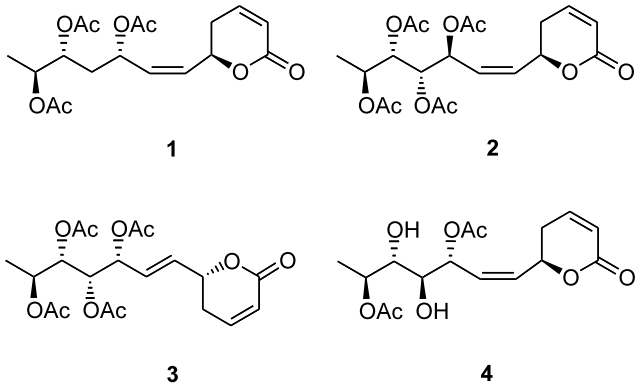
**Abstract**—The first total synthesis of the naturally occurring lactone (+)-hyptolide is described. Ethyl L-lactate was the chiral starting material. Key steps of this 15-step synthesis were a Brown's asymmetric allylation, a Carreira's asymmetric ethynylation and a ring closing metathesis. 

Lactone rings constitute a structural feature of many natural products.[1,2] Many naturally occurring lactones, most particularly those being α,β-unsaturated,[3] display pharmacologically relevant properties (e.g. antitumoral or else tumor-promoting activity). Among the latter, the α,β-unsaturated δ-lactones hyptolide (+)-**1**,[4] spicigerolide (−)-**2**,[5] anamarine (+)-**3**[6] and synrotolide **4**[7] have been isolated from several *Hyptis* species and other botanically related genera (Scheme 1). These compounds contain a polyoxygenated chain connected with an α,β-unsaturated six-membered lactone and have been found to show a range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity, etc. Spicigerolide (−)-**2**, for instance, has been found to exhibit cytotoxicity ($ED_{50}=1.5$ μg/mL) in the human nasopharyngeal carcinoma (KB) assay system.[5] Other structurally similar lactones from *Hyptis* and taxonomically related species have been found to be antimicrobial.[8] Such pharmacological properties make these compounds interesting synthetic goals. However, only for (+)-**3** and (−)-**3** have total syntheses been published so far.[9–11] Very recently, we have accomplished a stereoselective synthesis of (−)-**2** using L-rhamnose as the chiral starting material.[12]




**Scheme 1.**

Within our recently initiated program on the synthesis of natural lactones using ring-closing metathesis (RCM) reactions as one of the key steps,[12,13] we have now devised a stereoselective synthesis for (+)-**1**. The nature of the polyoxygenated chain of compounds **1**–**4** points to sugars as the starting materials. But while the configuration of the side chain in (−)-**2** suggested L-rhamnose,[12] the same synthetic strategy would require for (+)-**1** the commercially nonavailable sugar 3,6-dideoxy-L-glucose. Therefore, we envisaged a different retrosynthetic concept (Scheme 2). Aside from the RCM and stereoselective allylation steps already used in the synthesis of **2**,[12] we further needed here a stereoselective ethynylation of an O-protected β-hydroxy aldehyde. An interesting aspect of this synthetic route is that slight modifications in some of these steps should lead to stereoisomers of **1**, useful for investigations on relationships between structure and pharmacological activity.

The synthesis starts with the known chiral aldehyde **5** (Scheme 3), prepared in two steps from ethyl L-lactate.[14] Asymmetric allylation of **5** to homoallyl alcohol **6** was performed with Brown's B-allyl di*iso*pinocampheylborane,[15] prepared in turn from allylmagnesium

*Keywords*: (+)-hyptolide; ring-closing metathesis; asymmetric allylboration; asymmetric ethynylation; chiral pool.

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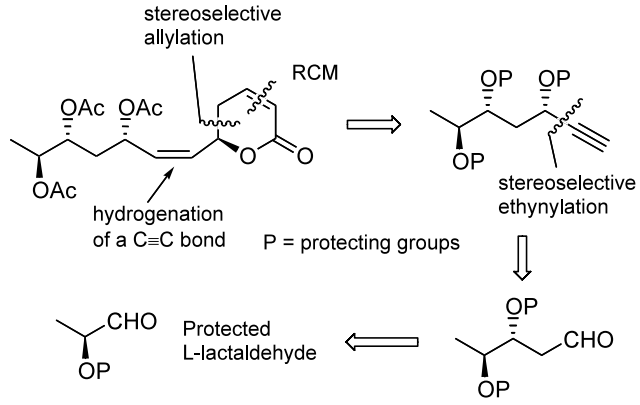
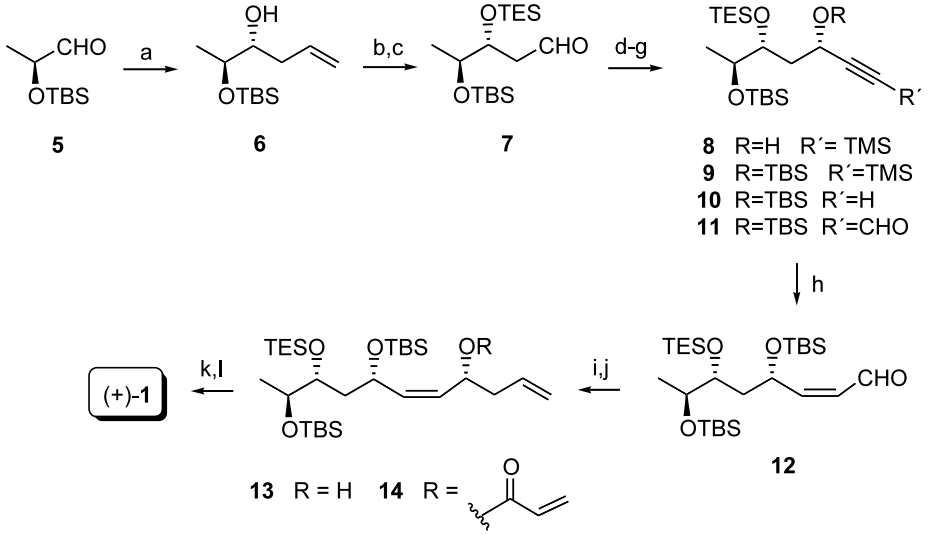



**Scheme 2.**

bromide and (+)-DIP-Cl (di*iso*pinocampheylboron chloride). Protection of the hydroxyl group as a TES derivative[16,17] was followed by oxidative cleavage of the olefinic bond to yield β-silyloxy aldehyde **7**. We then tested several ethynyl metal reagents on this aldehyde but no sufficiently stereoselective addition was achieved.[17] Finally, Carreira's asymmetric protocol[18–20] solved the problem and provided propargyl alcohol **8** as a single diastereomer. Alcohol silylation followed by selective cleavage of the C-silyl group furnished the terminal acetylene **10**, which was C-formylated to **11** via the intermediate lithium derivative.

Semihydrogenation of the C≡C bond in **11** was performed using Lindlar catalyst. *Z*-Enal **12** was subjected as above to Brown's asymmetric allylation, which provided here alcohol **13** as a single diastereomer. Acylation of **13** with acryloyl chloride furnished acrylate **14**, which was then subjected to RCM in the presence of 10% of Grubbs' standard catalyst $PhCH{=}RuCl_2(PCy_3)_2$.[21] The expected conjugated δ-lactone (like **1** but with the silyl protecting groups in place of the acetate residues) was formed in an excellent yield without addition of $Ti(OiPr)_4$ being necessary.[22] Finally, cleavage of all silyl groups and acetylation of the three hydroxyl functions (two operative steps but six functional transformations) was achieved in an excellent 83% yield to afford (+)-**1**, identical in its physical and spectral properties to the natural compound.[4,23]

In summary, a total synthesis of natural lactone (+)-**1** has been achieved in a highly stereoselective way using ethyl L-lactate as the starting material. Three C–C bonds were created by means of asymmetric reactions. Sizeable amounts of (+)-**1** have thus been made available for further pharmacological studies. Small modifications in the synthetic route described above (creation of a *trans* C=C bond, use of the enantiomeric $Ipc_2Ballyl$ reagent and/or *N*-methylephedrine) will lead to nonnatural diastereomers of the naturally occurring lactone, to be used for studies on structure–biological activity relationships. Such studies are now underway and will be disclosed in full in the near future.




**Scheme 3.** *Reaction conditions*: Reagents and conditions: (a) $AllylBIpc_2$ [prepared from allylmagnesium bromide and (+)-DIP-Cl], $Et_2O$, −78°C (82%, 92:8 diastereomeric mixture). (b) TESOTf, 2,6-lutidine, $CH_2Cl_2$, rt, 87%. (c) $OsO_4$ (cat.), NMO, *t*BuOH/THF/$H_2O$, then $NaIO_4$, aq. THF, 78%. (d) $TMSC{\equiv}CH$, $Zn(OTf)_2$, $Et_3N$, (−)-*N*-methylephedrine, tol, rt. (e) TBSOTf, 2,6-lutidine, 0°C, $CH_2Cl_2$. (f) $K_2CO_3$/MeOH, rt, 58% overall. (g) BuLi, THF, 0°C, then DMF, 70%. (h) $H_2$, Lindlar catalyst, 84%. (i) $AllylBIpc_2$ [from (+)-DIP-Cl], $Et_2O$, −78°C, (79%, single diastereomer). (j) Acryloyl chloride, $NEt_3$, cat. DMAP, $CH_2Cl_2$, rt, 70%. (k) 10% $PhCH{=}RuCl_2(PCy_3)_2$, $CH_2Cl_2$, Δ, 82%. (l) PPTS, aq. MeOH, 70°C, then $Ac_2O$, $Et_3N$, cat. DMAP, $CH_2Cl_2$, rt, 83%. Abbreviations: TMS, trimethylsilyl; TES, triethylsilyl; TBS, *t*-butyldimethylsilyl; Ipc, *iso*pinocampheyl; NMO, *N*-methylmorpholine *N*-oxide; DMAP, 4-dimethylaminopyridine; PPTS, pyridinium *p*-toluenesulfonate.

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