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Enantioselective Access to 2,7-Cis-Disubstituted Oxepanes: Formal Synthesis of (+)-Isolaurepan

M. Carmen Carreño,*,† Renaud Des Mazery,†,‡ Antonio Urbano,† Françoise Colobert,*,‡ and Guy Solladié*,‡

Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain, and Laboratoire de Stéréochimie associé au CNRS, Université Louis Pasteur, E.C.P.M., 25 rue Becquerel, 67087 Strasbourg Cedex 2, France

carmen.carrenno@uam.es

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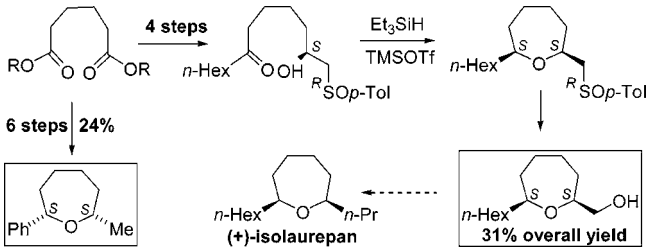
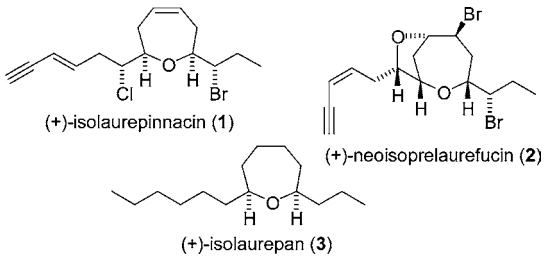
ABSTRACT



The asymmetric synthesis of 2,7-cis-disubstituted oxepanes bearing a sulfoxide is achieved from commercially available precursors in only five steps. The key step is the highly diastereoselective Et_3SiH/TMSOTf-promoted reductive cyclization of enantiopure hydroxysulfinyl aryl or alkyl ketones.

Seven-, eight-, and nine-membered medium ring ethers are a common structural unit of many ladder ether marine toxins and simpler *Laurencia* acetogenins metabolites,[1] but they are generally difficult to synthesize via standard cyclization methodologies.[2] Nevertheless, the challenge of their efficient construction has led to the development of several strategies for their synthesis,[1,3,4] mainly in racemic form.

(+)-Isolaurepinnacin (**1**)[5] and (+)-neoisoprelaurefucin (**2**)[6] are representative members of the *Laurencia*-derived C15 acetogenins containing an α,α′-cis-disubstituted oxepane ring. Although synthetic investigations toward the stereoselective construction of racemic cis-2,7-disubstituted-4,5-oxepenes and oxepanes have resulted in several reports,[7] only a few have dealt with nonracemic derivatives such as (+)-isolaurepan (**3**),[8] the fully saturated core of (+)-**1**, as well as other nonracemic oxepene[9] and oxepane[10] derivatives.



In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[11] we have recently reported a highly stereoselective approach to cis-2,5-disubstituted

† Universidad Autónoma de Madrid.
‡ Université Louis Pasteur.

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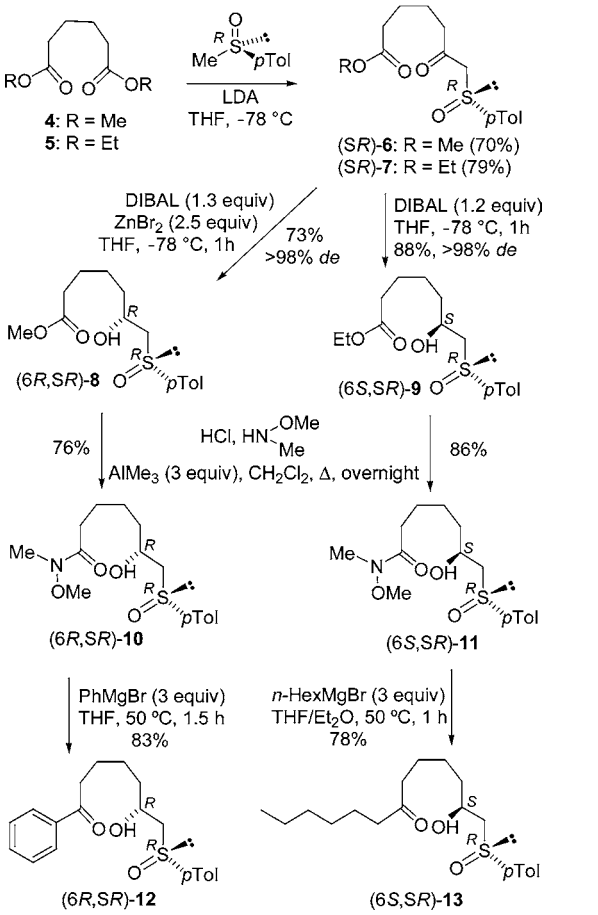
tetrahydrofuran and 2,6-disubstituted tetrahydropyran systems[12] based on the reductive cyclization of the corresponding enantiopure hydroxysulfinyl ketones using the Et_3SiH/TMSOTf system.[13] In this paper, we extend this methodology to the enantioselective synthesis of 2,7-cis-disubstituted oxepanes illustrating its usefulness with the short formal synthesis of (+)-isolaurepan (**3**).

The synthesis began with the condensation of the lithium anion derived from (S*R*)-methyl-*p*-tolylsulfoxide[14] and dimethyl (**4**) or diethyl adipate (**5**) to give enantiopure β-keto sulfoxides (S*R*)-**6** and (S*R*)-**7** in 70% and 79% yield, respectively (Scheme 1). Reduction of derivative **4** with DIBAL-H in the presence of $ZnBr_2$ afforded β-hydroxysulfoxide (6*R*,S*R*)-**8** in 73% yield with an excellent diastereoselectivity (de >98%). When DIBAL-H alone was used to reduce the ketosulfinyl ester **5**, compound (6*S*,S*R*)-**9** was exclusively formed in 88% yield. The synthesis of Weinreb's amides (6*R*,S*R*)-**10** and (6*S*,S*R*)-**11** was, respectively, achieved by treatment of esters **8** (76% yield) and **9** (86% yield based on 23% recovered starting material) with *N*-methyl methylhydroxylamine in the presence of an excess of $AlMe_3$.[15]

Scheme 1



Without protection of the OH group, amide **10** reacted with an excess of phenylmagnesium bromide in THF affording enantiopure aryl ketone (6*R*,S*R*)-**12** in 83% yield, whereas alkyl derivative (6*S*,S*R*)-**13** was obtained from **11** by treatment with *n*-hexylmagnesium bromide in THF/Et_2O in 78% isolated yield.

With hydroxysulfinyl ketones in hand, we tried the reductive cyclization conditions to access the cis-2,7-disubstituted oxepane ring. Thus, when phenyl ketone **12** was treated with 10 equiv of triethylsilane followed by 1.5 equiv of trimethylsilyl triflate in CH_2Cl_2 at 0 °C, oxepane (2*S*,7*R*,S*R*)-**14** was formed in only 30 min as the exclusive diastereoisomer and isolated in 83% yield (Scheme 2). The relative cis configuration of this derivative was initially assigned from the NOESY enhancements observed between H_2 and H_7 protons in **14** and later by the chemical correlation with racemic known compound **15**.

Finally, the treatment of sulfoxide **14** with Raney nickel in EtOH at room temperature gave rise to (2*S*,7*S*)-7-methyl-2-phenyloxepane (**15**) [$[\alpha]^{20}_D = -53$ (*c* 1, $CHCl_3$)], in 90% yield. This compound was shown to be identical, except in the α value, to the racemic derivative described by Nicolaou,[13] allowing us to confirm the cis stereochemistry of compound **14**.

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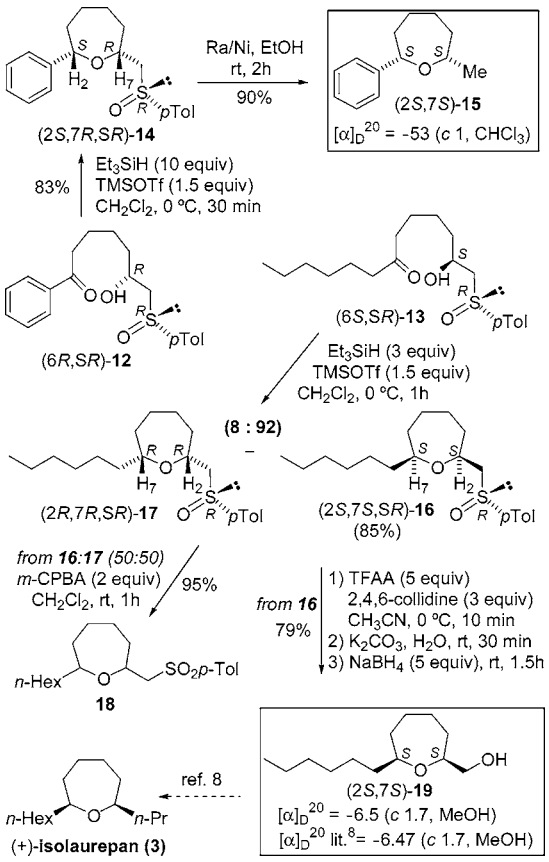
Scheme 2



When we applied the same Et_3SiH/TMSOTf conditions for the reductive cyclization of *n*-hexyl ketone **13**, a 92:8 mixture of diastereoisomers (2*S*,7*S*,S*R*)-**16** and (2*R*,7*R*,S*R*)-**17** was obtained after 1 h, from which major isomer **16** was isolated in 85% yield. The relative cis configuration of both derivatives was again assigned from the NOESY enhancements observed between H_2 and H_7 protons in **16** and **17**. Moreover, the *m*-CPBA oxidation of a 50:50 mixture of **16** and **17** afforded in 95% yield a unique sulfone **18**, confirming again the same relative configuration for the stereogenic carbons of **16** and **17**.

The absolute configuration of derivative **16** was ascertained after transformation into the known compound (−)-**19**. Thus, the treatment of **16** under the classical Pummerer reaction conditions[16] ((i) TFAA, 2,4,6-collidine; (ii) K_2CO_3) followed by reduction with $NaBH_4$ gave rise to the corresponding alcohol (2*S*,7*S*)-2-hexyl-7-(hydroxymethyl)oxepane (**19**) [$[\alpha]^{20}_D$ = −6.5 (*c* 1, $CHCl_3$)], in 79% yield. This compound was shown to be identical to that described in the literature[8] [$[\alpha]^{20}_D$ = −6.47 (*c* 1, $CHCl_3$)]. This synthetic sequence can be considered as a formal synthesis of (+)-isolaurepan (**3**), the fully saturated skeleton of the natural compound (+)-isolaurepinnacin (**1**), because derivative (−)-**19** had been previously transformed, after two steps, into compound (+)-**3**.[8]

In summary, the Et_3SiH/TMSOTf-promoted reductive cyclization of the corresponding hydroxysulfinyl aryl or alkyl ketones is an excellent pathway for the enantioselective construction of the cis-2,7-disubstituted oxepane core. The usefulness of the methodology has been demonstrated with the formal synthesis of (+)-isolaurepan (**3**) through the enantioselective preparation of the advanced intermediate (−)-**19** in only six steps from commercially available diethyl adipate with 31% overall yield.

Further applications of this method to the asymmetric synthesis of eight- and nine-membered medium ring ethers are now in progress.

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Supporting Information Available: Experimental procedures and data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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