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Synthesis of tetrahydrofuran lignans

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Abstract

This brief review details the racemic and enantioselective syntheses of naturally occurring tetrahydrofuran lignans burseran, dehydroxycubebin, brassilignan, and several analogs of the natural products. The key bond-forming strategies employed in these syntheses include Diels–Alder and nitrile–oxide cycloadditions, stereoselective alkylation, Michael additions, and radical cyclizations.

Key words: Tetrahydrofuran lignans, tubulin, spindle poisons, antitumor agents, platelet-activating factors, burseran, dehydroxycubebin, brassilignan, Michael additions, Diels–Alder reaction, dehydration, butyrolactones, nitrile oxide cycloadditions, and radical cyclization.

1. Introduction

Tetrahydrofuran lignans (9,9'-epoxylignans), a small subclass of lignan natural products, are of interest because of their widespread occurrence, varied biological activity, and use in folk medicine[1]. Several natural lignans and their analogs possess potent anti-tumor properties. Several lignans such as colchicine, podophyllotoxin, steganacin[2], and the tetrahydrofuran lignans burseran and dehydroxycubebin (Fig.1)[3] function as spindle poisons which prevent the normal function of the mitotic spindle. These compounds interact with the tubulin–microtubule system, the precursors for spindle formation[4]. Most of these compounds interfere with the tubulin microtubule system by binding with tubulin at different regions. The colchicine-binding site recognizes a number of natural and unnatural products containing two aromatic rings connected by a variety of structural elements, and it is a potential target site for the rational design of new antitubulin agents[4-6]. Therefore, a general methodology for the preparation of analogs, which have potential for binding at the colchicine site, is attractive for a structure–activity study. In addition to their anti-tumor activity[3a], the tetrahydrofuran lignans also exhibit platelet-activating factor antagonism[6] and diuretic[7] properties.

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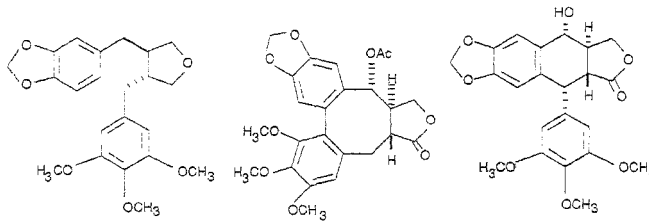


FIG. 1. Lignan natural products.

2. Review of the synthesis of tetrahydrofuran lignans

Several racemic and chiral routes for the synthesis of tetrahydrofuran lignan natural and unnatural products have been reported in the literature. This review will cover the total synthesis of lignan compounds in racemic form and also the enantioselective synthesis (+)-3,4-bis(benzyl)-tetrahydrofuran **1a**, (+)-brassilignan **1c**, (+)-dehydroxycubenin **1d**, and (+)-burseran **1e** as well as (−)-3,4-bis(benzyl)-tetrahydrofuran **2a**, (-)-brassilignan **1c**, (−)-dehydroxycubenin **1d**, and (−)-burseran **1e** (Fig. 2). A combination of methods (dehydration of substituted 1,4-diols, alkylation methodologies, Michael additions, Diels–Alder cycloaddition, nitrile oxide cycloaddition, and radical cyclization) that have previously been used to synthesize tetrahydrofuran lignans will also be discussed.

1 **2**

Entry	*Compound*	R_1	R_2
1a, 2a	3,4-Bis(benzyl)-tetrahydrofuran	Phenyl	Phenyl
1b, 2b	3,4-Bis(3-methoxybenzyl)-tetrahydrofuran	3-Methoxyphenyl	3-Methoxyphenyl
1c, 2c	Brassilignan	3,4-Dimethoxyphenyl	3,4-Dimethoxyphenyl
1d, 2d	Dehydroxycubebin	3,4-Methylenedioxyphenyl	3,4-Methylenedioxyphenyl
1e, 2e	Burseran	3,4-Methylenedioxyphenyl	3,4,5-Trimethoxyphenyl

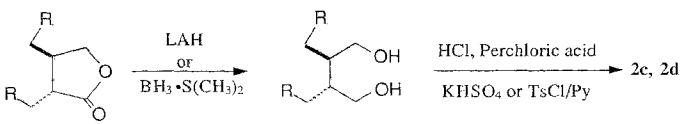
FIG. 2. Tetrahydrofuran lignans.

2.1. Dehydration of 1,4-butanediols from natural sources

Several groups have used the methodology shown in Scheme 1 to convert a lactone lignan natural product to a tetrahydrofuran lignan compound[8]. The reduction of lactone to a 1,4-butanediol followed by dehydration is a convenient method for constructing the tetrahydrofuran framework, and this procedure is useful for characterizing the starting natural product. Two different reducing reagents, lithium aluminium hydride and borane dimethylsulfide complex, are used in the first step; in the second step, dehydration may be carried out either under acidic conditions or by tosylation with *p*-toluenesulfonyl chloride (TsCl). In this manner, (–)- dimethylmatairesinol **3c** is transformed to (–)-brassilignan **2c**. Brassilignan is also a natural product which is isolable from the leaves of *Flindersia brassii*[9]. Similarly, dehydroxycubebin **2d** was transformed from the natural product cubebin **3d**.

An unusual diglucoside is isolated from the linseed meal of flaxseed and is converted to (+)-brassilignan **1c** in three steps (Scheme 2)[10]. In this procedure, the glucoside bonds are broken by sulfuric acid followed by methylation of the aromatic alcohols. In the last step of the synthesis, the 1,4-butanediol is dehydrated to give the tetrahydrofuran lignan.

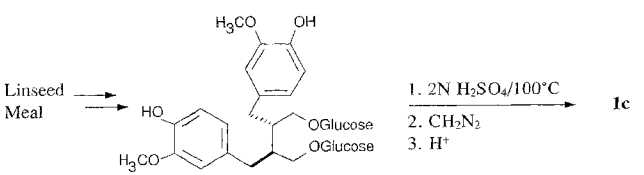
Phyllanthin (Scheme 3) was isolated from the leaves of *Phyllanthus niruri*, but could not be completely characterized until it was converted to (+)-brassilignan **1c**[11]. The structure and absolute stereochemistry of phyllanthin could then be determined by direct comparison with assilignan.



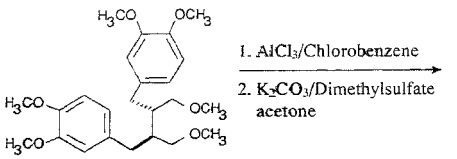
3c, 3d

(c) R = 3,4-Dimethoxyphenyl
(d) R = 3,4-Methylenedioxyphenyl

SCHEME 1.



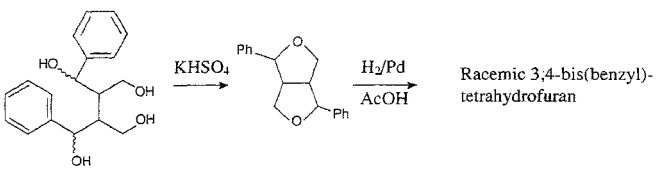
SCHEME 2.



SCHEME 3.

2.2. *Dehydration of 1,4-butanediols derived from alkylation methodology*

The dehydration methodology described in the previous section is also useful for 1,4-butanediols obtained through synthetic methods. The synthesis of racemic 3,4-bis(benzyl)tetrahydrofuran begins with the dehydration of the tetrol to form a furofuran compound. This bicyclic molecule was transformed to the product of interest by catalytic hydrogenation over palladium (Scheme 4)[12].



SCHEME 4.

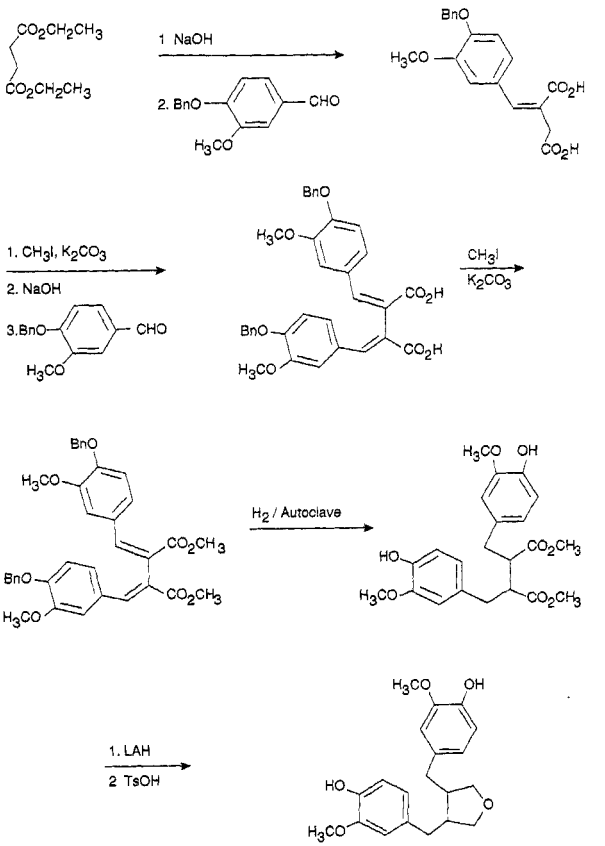
Matsuura and Iinuma[13] synthesized a derivative of brassilignan to aid in their characterization of the natural product (–)-divanillyltetrahydrofuran ferulate (Scheme 5). The synthesis of racemic 3,4-bis(4-hydroxy-3-methoxybenzyl)tetrahydrofuran was accomplished by two Stobbe condensations, two reductions, and a dehydration.

Hydrocinnamic acid is the starting material for the synthesis of racemic burseran shown in Scheme 6[14]. A two-step sequence was used to transform hydrocinnamic acid into a butanedioic acid compound. This dicarboxylic acid was then converted to a methyl ester, followed by lithium aluminum hydride reduction and acid dehydration to provide (±)-brassilignan.

Belletire *et al*[15] synthesized racemic burseran by a method similar to Scheme 6 (Scheme 7). Reaction of an iodo-substituted carboxylate with the dianion of hydrocinnamic acid in the presence of a copper (I) salt forms the butanedioic acid, which is converted to burseran.

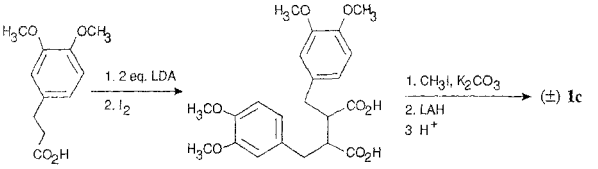
2.3. *Alkylation of a substituted γ-butyrolactone*

Tomioka and Koga[16] started with an optically pure 4-substituted-γ-butyrolactone **4** for the syntheses of optically pure *trans* and *cis* burserans (Schemes 8 and 9, respectively). In

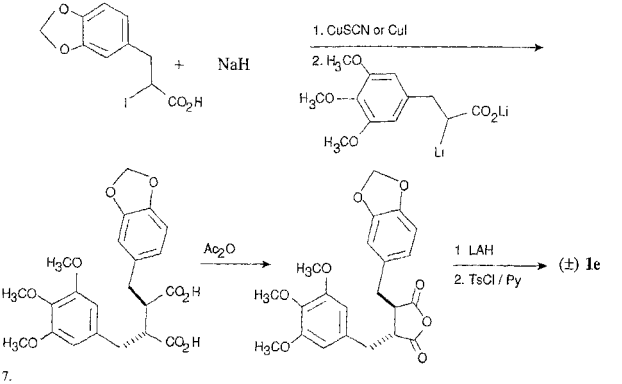


3,4-Bis(4-hydroxy-3-methoxybenzyl)tetrahydrofuran

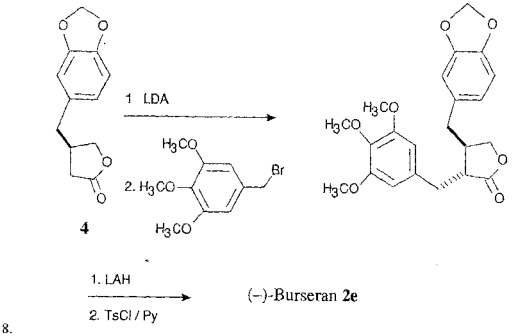
SCHEME 5.



SCHEME 6.

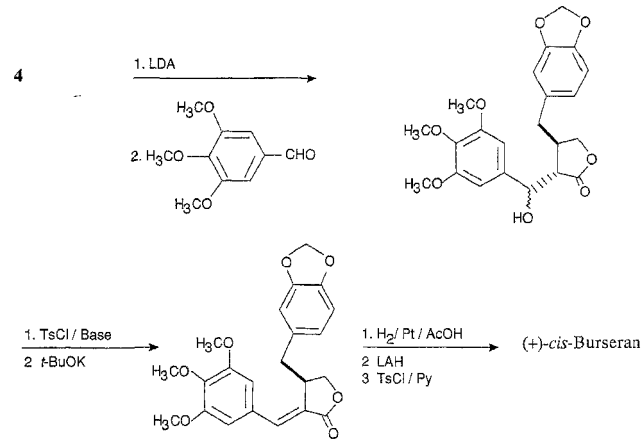


SCHEME 7.



SCHEME 8.

Scheme 8, the *trans* stereochemistry was established in the first step since the alkylation occurs from the least-hindered face of the molecule. *trans*-Burseran is the product after application of standard reduction and dehydration methodologies in lactone to tetrahydrofuran conversions. To synthesize *cis*-burseran (Scheme 9), the lactone anion from compound **4** is initially quenched with an aldehyde. The product alcohol is then converted to a tosylate to facilitate the transformation into an alkene. The *cis* stereochemistry was established by hydrogenation occurring from the least-hindered face of the molecule. If one were to start with the enantiomer of butyrolactone **4**, both (+)-*trans* and (–)- *cis* burserans could then be synthesized.

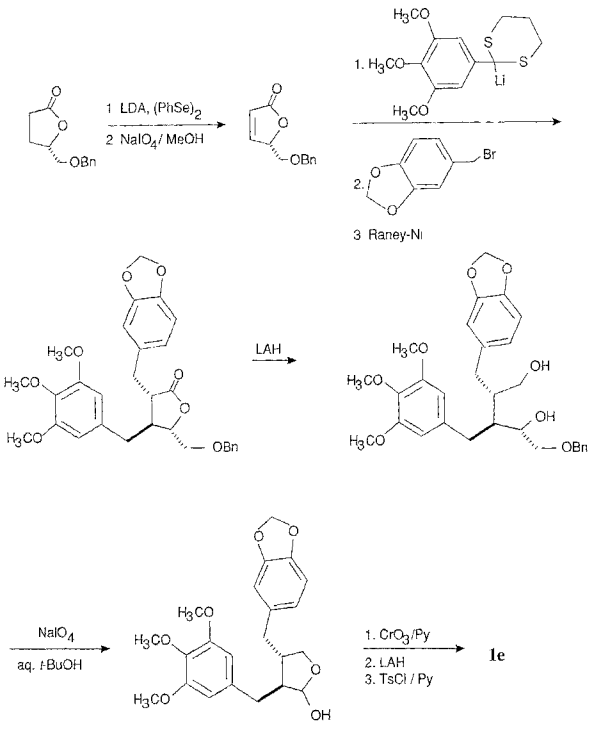


SCHEME 9.

2.4. Michael additions

Tomioka and Koga[16a,17] also employed an optically active γ-butyrolactone to synthesize (+)-burseran, but this synthesis began with a 5-substituted lactone (Scheme10). This methodology used the chiral center in the starting material to direct the stereochemistry at positions 3 and 4 for the synthesis of burseran. In the product obtained from the Michael addition, the groups in positions 3,4, and 5 are arranged to have the least steric interactions. Later in the synthesis, the initial chiral center of the 1,4-butanediol is lost during $NaIO_4$ oxidative cleavage to give the precursor for (+)-burseran.

For the synthesis of (–)-burseran and (–)-dehydroxycubebin, Magnusson and Rehnberg[18] used a Michael addition which involved an optically active 2,4-disubstituted-2,5-dihydrofuran **5** to introduce the appropriate substitutent on the tetrahydrofuran ring (Scheme 11). The *trans* stereochemistry at the 3 and 4 positions is established during the Michael addition. One

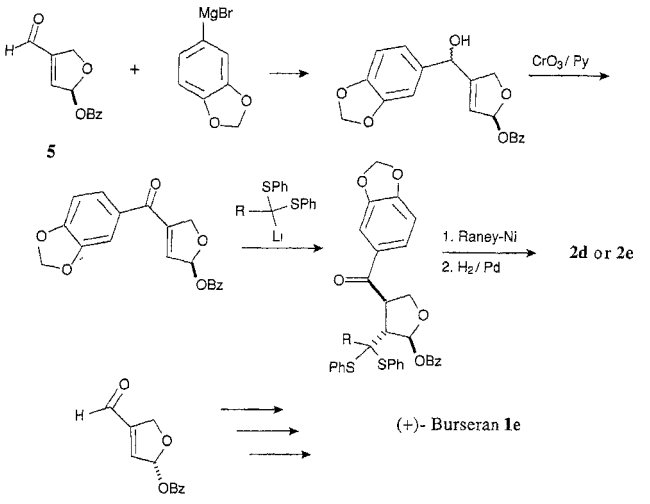


SCHEME 10

disadvantage of this methodology is that the starting material is prepared in six steps with poor overall yields (15 to 20%). (+)-Burseran was also synthesized using this methodology, starting instead with the enantiomer of compound **5** (Scheme 11).

2.5. Diels–Alder cycloaddition

The first synthesis of racemic *cis* and *trans* burseran was unique, because it was the only route which employed a Diels–Alder cycloaddition to construct the tetrahydrofuran framework (Scheme 12)[19]. Cole *et al*[20] used this synthesis to confirm their assigned structure of burseran, which they isolated from the plant *Bursera microphylla* (Burseraceae).



(d) R = Methylenedioxyphenyl
(e) R = 3,4,5-Trimethoxyphenyl

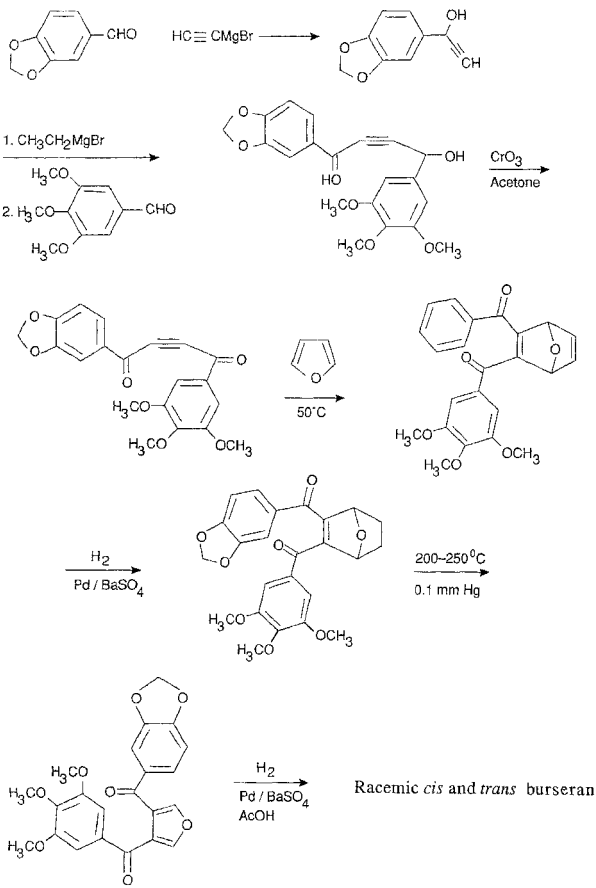
SCHEME 11.

2.6. *Nitrile oxide cycloaddition*

Gaboury and Sibi[21] recently reported a convenient route for the total synthesis of both enantiomers of several tetrahydrofuran lignans (Scheme 13). The lignans were synthesized by a convergent approach, which utilized a nitrile oxide cycloaddition to obtain 2,5-dihydrofurans. A lipase-mediated kinetic resolution of the alcohols **5** furnished both enantiomers of the lignan precursors in high optical purity (>99% ee). This was followed by an S_N2 displacement of the tosylate in **8** and **9** by α-lithiobenzyl-phenylsulfides. Both enantiomers of 3,4-bis(benzyl) tetrahydrofuran (**1a, 2a**), 3,4-bis(3-methoxy-benzyl)tetrahydrofuran (**1b, 2b**), brassilignan (**1c, 2c**), dehydroxycubebin (**1d, 2d**), and burseran (**1e, 2e**) were synthesized in overall yields of 6 to 16%. This methodology allows for flexibility in the choice of R_1 and R_2 by varying either the nitrile oxide or the benzylphenylsulfide.

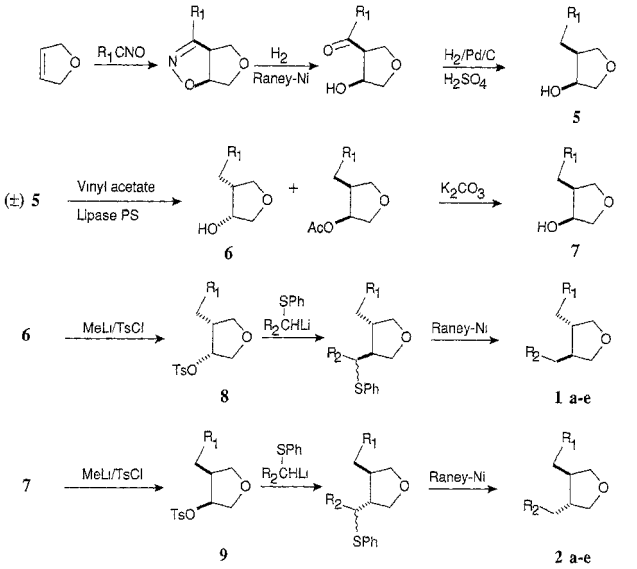
2.7. *Radical cyclization*

Hanessian and Leger[22] reported another novel approach to burseran and dehydroxycubebin in which they synthesized the tetrahydrofuran framework through a radical-mediated carbocyclization (Scheme 14). This methodology also utilized an aldehyde functionality (from the stannane



Racemic *cis* and *trans* burseran

SCHEME 12.



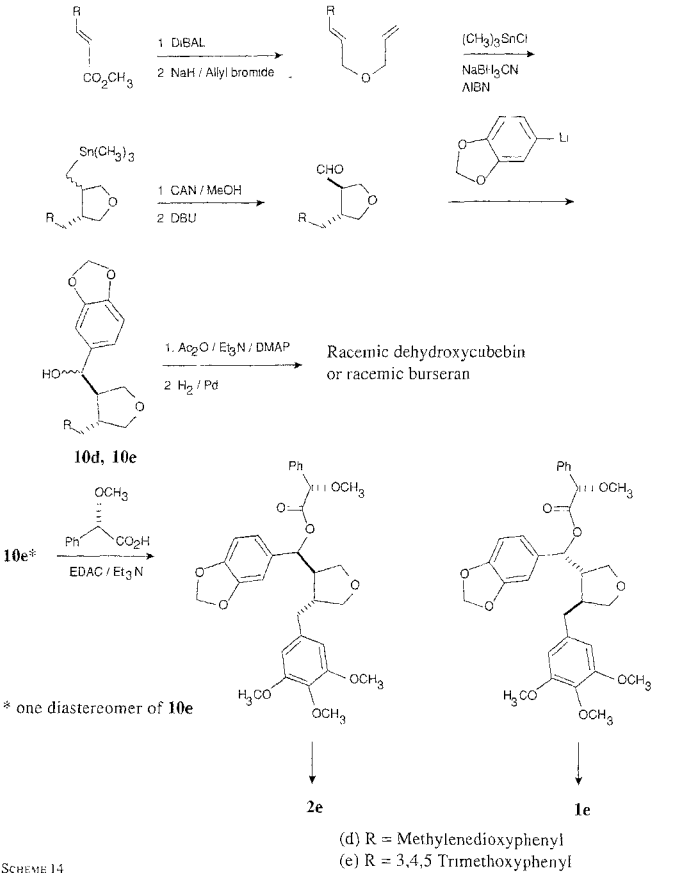
(a) $R_1 = R_2$ = Phenyl; (b) $R_1 = R_2$ = 3-Methoxyphenyl
(c) $R_1 = R_2$ = 3,4-Dimethoxyphenyl; (d) $R_1 = R_2$ = 3,4-Methylenedioxyphenyl
(e) R_1 = 3,4-Methylenedioxyphenyl, R_2 = 3,4,5-Trimethoxyphenyl

SCHEME 13.

precursor) to establish the *trans* stereochemistry at the 3 and 4 positions. Further reactions on this aldehyde furnished racemic burseran and dehydroxycubebin. The epimers of **10e** were then separated by flash column chromatography. One epimer of **10e** was esterified with *(S)*-O-methyl-mandelic acid to give the easily separable diastereomers. These esters can be individually cleaved by hydrogenation to yield the optically pure burserans.

3. Conclusions

This review illustrates several novel strategies for the total synthesis of biologically active tetrahydrofuran natural and unnatural products. The bond construction tactics utilized for the syntheses of these compounds should lay a foundation for the preparation of novel analogs for structure–activity studies.



SCHEME 14

Acknowledgement

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