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Enantioselective synthesis of functionalized 1-benzoxepines by phenoxide ion-mediated 7-*endo-tet* carbocyclization of cyclic sulfates[#]

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Dedicated to Professor Goverdhan Mehta on his 65th birthday

Keywords: 1-Benzoxepine / Sharpless asymmetric dihydroxylation / Cyclic sulphate

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Asymmetric synthesis of 2,3-disubstituted-1-benzoxepines is described. Key steps include Sharpless asymmetric dihydroxylation of *trans*-α,β-unsaturated esters and phenoxide ion-mediated intramolecular 7-*endo-tet* carbocyclization of *syn*-2,3-dihydroxy ester-derived cyclic sulphates.

Introduction

1-Benzoxepine is an important benzo-fused medium ring heterocycle because there are numerous biologically active natural products[1] and synthetic molecules[2] which contain this structural framework. Thus, synthesis of 1-benzoxepine derivatives constitutes an important objective in modern organic synthesis.[3] Following our interest in the field of enantioselective synthesis of biologically important heterocycles, we recently employed naturally occurring α-amino acids and Sharpless asymmetric dihydroxylation as the source of chirality to generate a large array of heterocylic molecules including natural and natural product like molecules.[4] As part of our research programme in this field, we sought to develop a synthetic route that could provide enantiomerically pure natural product like small molecules **1-6** containing 1-benzoxepine framework [Figure (1)].

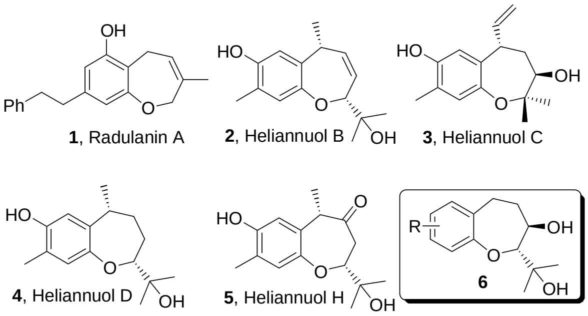


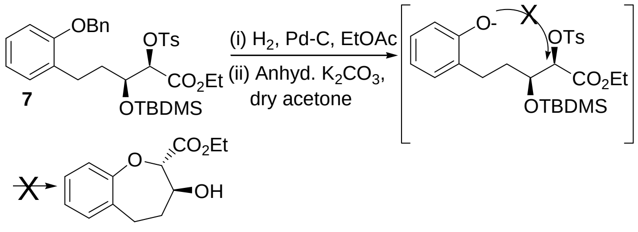
Figure 1. Selected natural products **1-5** and our designed target molecules **6** containing 1-benzoxepine ring system.

Results and Discussion

In a recent paper[4b] we have reported that asymmetric synthesis of 2,3-disubstituted-1-benzoxepine derivative could not be achieved *via* a phenoxide ion-mediated intramolecular S_N2 displacement of tosyloxy group of a β-hydroxy-α-tosyloxy ester derivative possibly due to an entropy factor [Scheme (1)]. This unsuccessful synthesis of 2-substituted-1-benzoxepine derivative prompted us to search for an alternate synthetic route.

Scheme 1. The unsuccessful synthesis of 2-substituted-1-benzoxepine derivative

Cyclic sulfates have been known for a long time, and the use of these compounds has been the subject of several reviews.[5] They are like epoxides but have higher reactivity.[6] High reactivity of these compounds as nucleophile acceptors is well known. While several synthetic utilizations of cyclic sulfates are known, their use for the enantioselective preparation of heterocycles has not been explored in depth. For example, cyclic sulfates have only been used as intramolecular *O*-alkylation substrates for the construction of tetrahydrofuran and tetrahydropyran rings.[7] Although it is well known that the intramolecular cyclization of tetrahedral system generally proceeds *via* an *exo*-cyclization pathway,[8] the pioneering report[7e] by Sharpless *et al* suggested that the relatively unstrained cyclic sulfate could permit *endo* cyclization in preference to *exo* cyclization. Taking into account of all these facts and our interest in the asymmetric synthesis of benzoannulated heterocycles,[4] we describe in this commuinication our preliminary results that illustrate a new asymmetric synthesis of 2,3-disubstituted-1-benzoxepines utilizing phenoxide ion-mediated intramolecular 7-*endo-tet* S_N2 carbocyclization of *syn*-2,3-dihydroxy ester-derived cyclic sulphates as the key step.



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In our study, commercially available 2-hydroxy-5-methoxybenzaldehyde **9a,** 2-hydroxy-3-methoxybenzaldehyde **9b** and 2-hydroxybenzaldehyde **9c** were selected as model starting materials. Compounds **9a-c** were converted into the corresponding phenolic –OH protected and two-carbon homologated aldehydes **12a-c** by essentially following the steps as depicted in Scheme 2. Thus, Wittig olefination of **9a-c** with (carbethoxymethylene)triphenylphosphorane in dry CH_2Cl_2 at room temparature furnished the corresponding *trans* cinnamate esters **10a-c** in very high yields**.** Next, hydrogenation of **10a-c** in the presence of 10% Pd-C followed by benzylation of the resulting hydroxy esters with benzyl bromide and anhydrous K_2CO_3 in dry

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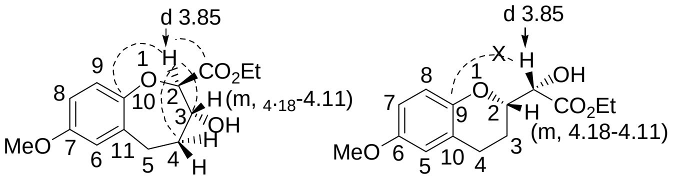
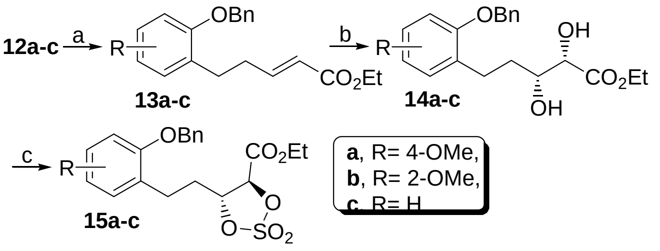
acetone under reflux condition yielded **11a-c** in high yields. DIBAL-H reduction of **11a-c** in dry toluene at -78°C furnished the corresponding aldehydes **12a-c** in very high yield.



16a **16a'**

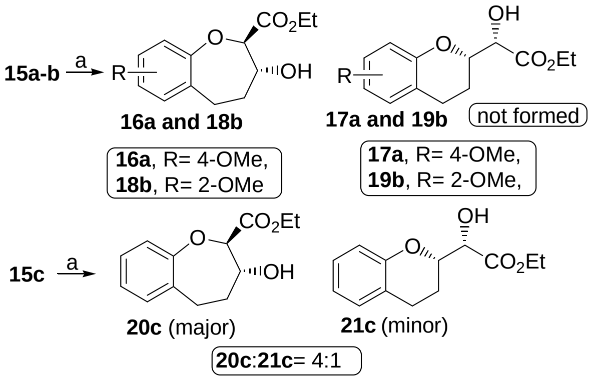
Scheme 2. *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 1h, **10a** (96%), **10b** (95%) and **10c** (95%). (b) (i) H_2, 10%Pd-C, EtOAc, 8 h, (ii) BnBr, anhyd. K_2CO_3, dry acetone, reflux, 4h, **11a** (90%), **11b** (87%) and **11c** (91%); for combined two steps. (c) DIBAL-H, dry toluene, -78°C, 1h, **12a** (95%), **12b** (94%) and **12c** (95%).

With the ready availability of aldehydes **12a-c**, attention was turned to their elaboration into cyclic sulfate derivatives [Scheme (3)]. Towards that objective, **12a-c** were treated with (carbethoxymethylene)triphenylphosphorane in dry CH_2Cl_2 at room temperature to obtain the corresponding *trans* unsaturated esters **13a-c**. Subjection of **13a-c** to Sharpless asymmetric dihydroxylation[9] with AD mix β in ^{t}BuOH–H_2O (1:1) at 0°C for 24 h furnished enantiopure dihydroxyl derivatives **14a-c** in good yields and high enantiomeric excess (90%, ee >99%; determined by chral HPLC analysis). Treatment of diol **14a-c** with thionyl chloride and triethylamine in CH_2Cl_2 gave the respective cyclic sulfites which were further oxidized using $NaIO_4$ and a catalytic amount of ruthenium trichloride to furnish the corresponding cyclic sulfates **15a-c** in good yields.



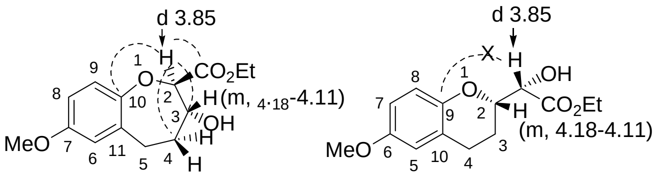
Scheme 3. *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, overnight, **13a** (80%), **13b** (82%) and **13c** (77%). (b) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 24 h, **14a** (95%), **14b** (94%) and **14c** (88%). (c) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 20 min (ii) $RuCl_3$, $NaIO_4$, MeCN–H_2O; 1:9, 0 °C, 10 h, **15a** (84%), **15b** (87%) and **15c** (85%); for combined two steps.

With cyclic sulfates **15a-c** in hand, we turned our attention to phenoxide ion-directed intramolecular cyclic sulfate ring opening reaction [Scheme (4)]. Accordingly, **15a-c** were first debenzylated under a hydrogen atmosphere in the presence of 10% Pd-C to furnish the corresponding phenolic derivatives which, without further purification, were treated with anhydrous K_2CO_3 in dry acetone and subsequently with 20% H_2SO_4 in THF.[10] After extensive NMR studies (^{1}H, ^{13}C, COSY, HMBC, HSQC), we were very delighted to observe that cyclic sulfates **15a-b** furnished the respective cyclic products **16a** and **18b** which contain 1-benzoxepine skeleton. It is important to mention that in the cyclization reaction of the two cyclic sulfates **15a-b** did not provide corresponding products **17a** and **19b** with 1-benzopyran ring system**.** However, cyclic sulfate **15c** furnished major cyclic product **20c** containing a 1-benzoxepine skeleton (60%) and minor product **21c** (15%) with a benzopyran ring system. To the best of our knowledge this is the first use of α,β-dihydroxy ester cyclic sulfates in benzo-fused heterocycle synthesis.



Scheme 4. *Reagents and conditions*: (a) (i) H_2, 10%Pd-C, EtOAc, 8 h, 89%. (ii) anhyd. K_2CO_3, dry acetone, rt, 8h. (iii) 20% H_2SO_4, THF, rt,overnight, **16a** (70%), **18b** (72%) and **20c** (60%) and **21c** (15%); for combined three steps.

^{1}H NMR Spectrum of **16a** showed the presence of two multiplets at δ 2.34-2.25 and 1.65-1.52 attributable to the protons H-4$_a$ and H-4$_b$ and another multiplet at δ 2.89-2.65 due to two H-5 protons. H-3 appeared as a multiplet at δ 4.18-4.11 whereas the proton H-2 showed a doublet at δ 3.85 (J = 9.2). The presence of the –OH group was indicated by a broad singlet at δ 3.11. The above attribution of various protons was done by incisive analysis of COSY spectrum of **16a**. Based on the coupling observed in the HSQC spectrum of **16a**, ring carbons appearing at δ 83.9, 71.9, 33.4 and 28.0 were attributed to C-2, C-3, C-4 and C-5, respectively. Similarly, the signals at δ 61.6, 55.4, and 14.0 were assigned to the –O$\underline{C}$H$_2$CH$_3$, -O$\underline{C}$H$_3$ and –OCH$_2\underline{C}$H$_3$ respectively.



16a **17a**

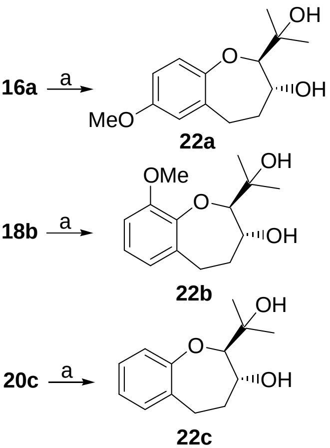
Figure 2. Coupling of H-2 in the HMBC spectrum of **16a**

Finally, six signals at δ 156.0, 151.9, 135.6, 121.8, 115.0, and 112.1 were assigned to the aromatic carbons C-7, C-10, C-11, C-8, C-6 and C-9. In the HMBC spectrum of **16a**, H-2 [δ 3.85 (J = 9.2)] showed coupling with $\underline{C}$=O (δ 170.7), C-3 (δ 71.9), C-4 (δ 33.4) and C-10 (δ 151.9) [Figure (2)]. The long range coupling of H-2 with C-10 confirmed our hypothesis of 1-benzoxepine ring formation over 1-benzopyran ring formation as this coupling would not be possible in case of **17a.** Again, had the cyclic product been **17a**, the proton [δ 4.18-4.11 (m, 1H)] would have shown long range coupling with the aromatic carbon atom [C-9 (δ 151.9) in structure **17a**] which is completely absent in the HMBC spectrum. Thus, the 1-benzoxepine structure **16a** was confirmed. The structures of other isolated cyclic products **18b**, **20c** and **21c** were similarly assigned.

It is a well known fact that due to the presence of ester group, the α-carbon atom of an α,β-dihydroxy ester-derived cyclic sulfate possesses higher reactivity than the β-carbon and hence nucleophilic attack occurs at α-carbon almost exclusively.[5b] Thus, formation of 1-benzoxepine derivatives **16a**, **18b** and **20c** (*via* 7-*endo-tet* cyclization) might be explained on the basis of high reactivity at α-carbon. At the same time, 1-benzopyran derivatives **17a, 19b** and **21c** (formed *via* 6-*exo-tet* cyclization) might be considered as entropically favouable. Since the presence of methoxy group *ortho*- and *para*- to a phenolic –OH functionality on a phenyl ring increases the nucleophilicity of the phenoxide ion, cyclic sulfates **15a-b** gave only 1-benzoxepine derivatives **16a**, **18b** and **20c**. In the absence of methoxy group nucleophilicity of a phenoxide ion gets reduced. Thus, cyclic sulfate **15c** furnished 1-benzoxepine derivative **20c** along with minor amount of 1-benzopyran derivative **21c**.

Finally, treatment of **16a**, **18b** and **20c** with an excess of methylmagnesium iodide furnished the corresponding tertiary alcohols **22a-c** in high yields, Scheme 5.

Scheme 5. *Reagents and conditions*: (a) MeMgI, dry THF, 0ºC-reflux, 3h, **22a** (88%), **22b** (90%) and **22c** (94%); for combined two steps.



Conclusions

In summary, in the present communication we describe an asymmetric synthesis of 2,3-disubstituted 1-benzoxepines by an easy and high yielding reaction sequence. Key steps include Sharpless asymmetric dihydroxylation reaction on suitable α,β-unsaturated esters and construction of the 1-benzoxepine nuclei by phenoxide ion-directed intramolecular 7-*endo-tet* carbocyclization of *syn*-2,3-dihydroxy ester-derived cyclic sulphates. Presence of methoxy groups *ortho*- and *para*- to the phenolic –OH functionality on the phenyl ring rendered the cyclization reaction completely regioselective producing 1-benzoxepine derivatives only. In the absence of a methoxy group on the phenyl ring, the reaction furnished both 1-benzoxepine and 1-benzopyran derivatives with the former being the major one. A systematic study of the effect of different substituents at different positions of the phenyl ring on the key cyclization reaction and the utilization of the same reaction in the synthesis of other benzo-fused oxa-heterocycles of different ring size is underway in our laboratory and will be reported in due course as a full paper with complete structure-reactivity relationships.

Experimental Section

(2*R*,3*R*)-ethyl 3-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzo[b]oxepine-2-carboxylate (16a):

To a stirred solution of **15a** (0.9 g, 2.06 mmol) in ethyl acetate (20 mL) was added 10% Pd-C (50 mg). After stirring for 3 h at room temperature under pressure of a hydrogen balloon, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to get the corresponding debenzylated product (0.64 g) as a colorless semi-solid which was used for the next step without further purification.

To a stirring solution of the above debenzylated product in dry acetone (20 mL), was added anhyd. K_2CO_3 (0.4 g, 2.89 mmol) and the mixture was stirred for 5 h at room temperature. After removing acetone of the raction mixture under reduced pressure, the residue was stirred with 20% aq H_2SO_4 (20 mL) and THF (10 mL) for 16 h. The resultant solution was then neutralised with aq. saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic phases were washed with water, brine dried Na_2SO_4, and concentrated. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in hexane) furnished **16a** as a colorless semi-solid (0.384 g, 70%; for combined three steps). $[\alpha]^{25}_{D}$ +65.38 (*c* 4.11, $CHCl_3$). IR (KBr): 3434, 2923, 2358, 1648, 1511, 1218, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.01-6.98 (m, 1H), 6.67-6.64 (m, 2H), 4.30 (q, 2H, $J = 7.1$), 4.18-4.11 (m, 1H), 3.85 (d, 1H, $J = 9.2$), 3.75 (s, 3H), 3.11 (s, br, 1H), 2.89-2.65 (m, 2H), 2.34-2.25 (m, 1H), 1.65-1.52 (m, 1H), 1.35 (t, 3H, $J = 7.1$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 156.0, 151.9, 135.6, 121.8, 115.0, 112.1, 83.9, 71.9, 61.6, 55.4, 33.4, 28.0, 14.0. MS (FAB): *m/z* 266 $[M]^+$. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.31; H, 6.66.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and analytical data of selected compounds.

Acknowledgments

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[10] Enantiomeric excess (ee) values of **16a**, **18b** and **20c** were determined by derivatizing them as the Mosher's ester and analyzing the corresponding ^{1}H NMR spectrum. The ee's were found to be >99%..

Eur. J. Org. Chem. 2009(2), 204-207

Entry for the Table of Contents

Layout 1:

Enantioselective Synthesis

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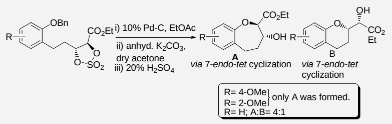

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