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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 sulfate

A new 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 sulfates.

Introduction

1-Benzoxepine is an important benzo-fused medium-sized 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 sources of chirality to generate a large array of heterocyclic 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 of general structure **6** containing the 1-benzoxepine framework (Figure 1).

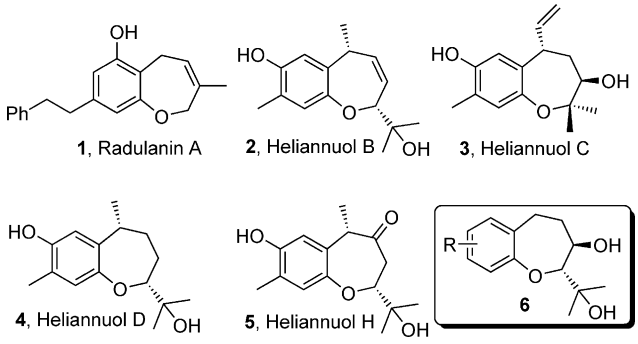
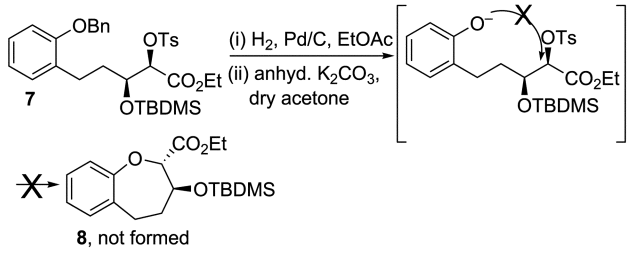


Figure 1. Selected natural products **1**–**5** and our designed target molecules **6** containing the 1-benzoxepine ring system.

Results and Discussion

In a recent paper[4b] we have reported that asymmetric synthesis of 2,3-disubstituted 1-benzoxepine derivative **8** could not be achieved by a phenoxide ion mediated intramolecular S_N2 displacement of the tosyloxy group of a β-hydroxy-α-tosyloxy ester derivative possibly due to an entropy factor (Scheme 1). This unsuccessful synthesis of 2,3-disubstituted 1-benzoxepine derivatives prompted us to search for an alternative synthetic route.



Scheme 1. 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 a higher reactivity.[6] The high reactivity of these compounds as nucleophile

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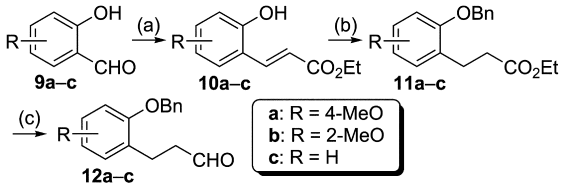
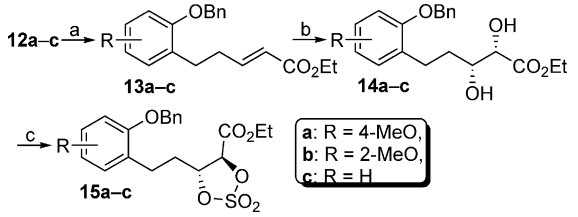
acceptors is well known. Whereas several synthetic utilizations of cyclic sulfates are known, their use for the enantioselective preparation of heterocycles has not been explored in depth. For example, cyclic sulfates have only been used as intramolecular *O*-alkylation substrates for the construction of tetrahydrofuran and tetrahydropyran rings.[7] Although it is well known that the intramolecular cyclization of a tetrahedral system generally proceeds by 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 benzo-annulated 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 sulfates as the key step.

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 phenol-protected and two-carbon-homologated aldehydes **12a**–**c** by essentially applying the steps as depicted in Scheme 2. Thus, Wittig olefination of **9a**–**c** with (ethoxycarbonylmethylene)triphenylphosphorane in dry CH_2Cl_2 at room temparature furnished the corresponding (*E*)-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 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.



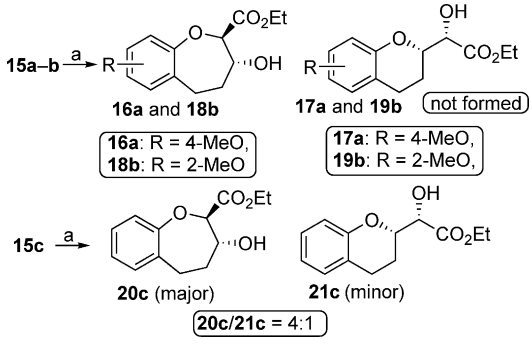
Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, room temp., 1 h, **10a** (96%), **10b** (95%) and **10c** (95%). (b) (i) H_2, 10% Pd/C, EtOAc, 8 h, (ii) BnBr, anhyd. K_2CO_3, dry acetone, reflux, 4 h, **11a** (90%), **11b** (87%) and **11c** (91%) for combined two steps. (c) DIBAL-H, dry toluene, –78 °C, 1 h, **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 (ethoxycarbonylmethylene)triphenylphosphorane in dry CH_2Cl_2 at room temperature to obtain the corresponding (*E*)-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 dihydroxy derivatives **14a**–**c** in good yields and high enantiomeric excess (90%, *ee* >99%; determined by chiral HPLC analysis). Treatment of diols **14a**–**c** with thionyl chloride and triethylamine in CH_2Cl_2 gave the respective cyclic sulfites, which were further oxidized with $NaIO_4$ 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, room temp., 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 the phenoxide ion directed intramolecular cyclic sulfate ring opening reaction (Scheme 4). Accordingly, **15a**–**c** were first debenzylated under hydrogen in the presence of 10% Pd/C to furnish the corresponding phenol 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 (^1H, ^{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 the 1-benzoxepine skeleton. It is important to mention that in the debenzylation/cyclization reaction sequence, cyclic sulfates **15a**,**b** did not provide the corresponding products **17a** and **19b** with the 1-benzopyran ring system. However, cyclic sulfate **15c** furnished the major cyclic product **20c** containing a 1-benzoxepine skeleton (60%) and the 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, room temp., 8 h, (iii) 20% H_2SO_4, THF, room temp., overnight, **16a** (70%), **18b** (72%) and **20c** (60%) and **21c** (15%) for combined three steps.

The ^1H NMR spectrum of **16a** showed the presence of two multiplets at δ = 2.34–2.25 and 1.65–1.52 ppm attributable to the protons 4-H^a and 4-H^b and another multiplet at δ = 2.89–2.65 ppm due to two 5-H protons; 3-H appeared

as a multiplet at δ = 4.18–4.11 ppm, whereas the proton 2-H showed a doublet at δ = 3.85 (J = 9.2 Hz). The presence of the OH group was indicated by a broad singlet at δ = 3.11 ppm. The above assignment of various protons was done by incisive analysis of a COSY spectrum of **16a**. Based on the coupling observed in the HSQC spectrum of **16a**, signals of ring carbon atoms appearing at δ = 83.9, 71.9, 33.4 and 28.0 ppm 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 ppm were assigned to OCH_2CH_3, OCH_3 and OCH_2CH_3, respectively.

Finally, six signals at δ = 156.0, 151.9, 135.6, 121.8, 115.0, and 112.1 ppm were assigned to the aromatic carbon atoms C-7, C-10, C-11, C-8, C-6 and C-9. In the HMBC spectrum of **16a**, 2-H [δ = 3.85 (J = 9.2 Hz)] showed coupling with C=O (δ = 170.7 ppm), C-3 (δ = 71.9 ppm), C-4 (δ = 33.4 ppm) and C-10 (δ = 151.9 ppm) (Figure 2). The long-range coupling of 2-H with C-10 confirmed our hypothesis of 1-benzoxepine ring formation over 1-benzopyran ring formation, as this coupling would not be possible in the case of **17a**. Again, had the cyclic product been **17a**, the 2-H [δ = 4.18–4.11 (m, 1 H) ppm] would have shown a long-range coupling with the aromatic carbon atom C-9 (δ = 151.9 ppm 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.

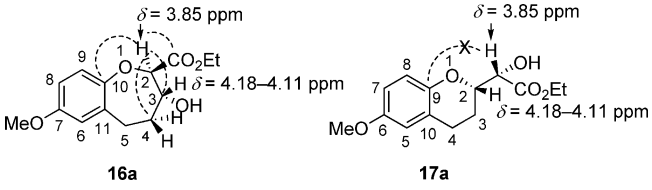
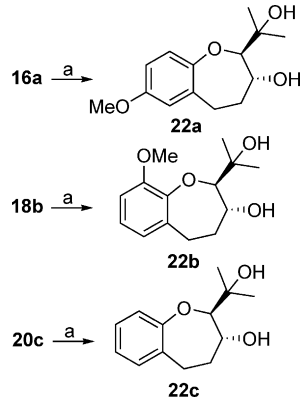


Figure 2. Coupling of 2-H in the HMBC spectrum of **16a**.

It is a well known fact that due to the presence of an ester group, the α-carbon atom of an α,β-dihydroxy ester derived cyclic sulfate possesses a higher reactivity than the β-carbon atom, and hence nucleophilic attack occurs at the α-carbon atom almost exclusively.[5b] Thus, formation of 1-benzoxepine derivatives **16a**, **18b** and **20c** (by 7-*endo*-*tet* cyclization) might be explained on the basis of the high reactivity at the α-carbon atom. At the same time, 1-benzopyran derivatives **17a**, **19b** and **21c** (formed by 6-*exo*-*tet* cyclization) might be considered as entropically favoruable. Since the presence of methoxy groups *ortho* and *para* to a phenol functionality on a phenyl ring increases the nucleophilicity of the corresponding phenoxide ion, cyclic sulfates **15a**–**b** gave only 1-benzoxepine derivatives **16a**, **18b** and **20c**. In the absence of a methoxy group, the nucleophilicity of a phenoxide ion is reduced. Thus, cyclic sulfate **15c** furnished 1-benzoxepine derivative **20c** along with a 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, 0 °C to reflux, 3 h, **22a** (88%), **22b** (90%) and **22c** (94%).

Conclusions

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 ring by phenoxide ion directed intramolecular 7-*endo*-*tet* carbocyclization of *syn*-2,3-dihydroxy ester derived cyclic sulfates. The presence of methoxy groups *ortho* and *para* to the phenol 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 oxaheterocycles of different ring size is underway in our laboratory and will be reported in due course with complete structure–reactivity relationships.

Experimental Section

Ethyl (2*R*,3*R*)-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 at room temperature under the pressure of a hydrogen balloon for 3 h, the reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure to yield the corresponding debenzylated product (0.64 g) as a colorless semi-solid which was used for the next step without further purification. To a stirred 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 at room temperature for 5 h. After removal of the acetone from 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). $[\alpha]_D^{25}$ = +65.38 (*c* = 4.11, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3434, 2923, 2358, 1648, 1511, 1218, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.01–6.98 (m, 1 H), 6.67–6.64 (m, 2 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 4.18–4.11 (m, 1 H), 3.85 (d, *J* = 9.2 Hz, 1 H), 3.75 (s, 3 H), 3.11 (br. s, 1 H), 2.89–2.65 (m, 2 H), 2.34–2.25 (m, 1 H), 1.65–1.52 (m, 1 H), 1.35 (t, *J* = 7.1 Hz, 3 H) ppm. ^{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 ppm. MS (FAB): *m*/*z* = 266 $[M]^+$. $C_{14}H_{18}O_5$ (266.29): calcd. 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.

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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 ^1H NMR spectrum. The *ee* values were found to be >99%.

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