Ozonolyses of Enantiopure 4-Alkoxy-3,6-dihydro-2*H*-1,2-oxazines: An Expedient Route to Functionalized α-Amino-β-hydroxy Esters

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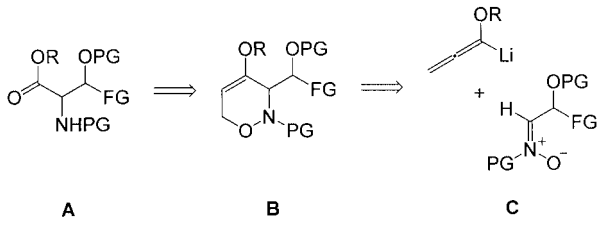
Ozonolysis and subsequent in situ acylation/base treatment converted the enantiopure carbohydrate-derived 1,2-oxazines **1**, **5**, **8** (either *syn*- or *anti*-configured) and *anti*-**11** into the highly functionalized α-amino-β-hydroxy esters **2**, **6**, **9** and **12** in moderate to good yields. Ketals of 5-hydroxylated 1,2-oxazines (e.g., *syn*-**3**) were formed as side products in most cases; the reactions of precursors *syn*- and *anti*-**8** even provided the ketals *syn*- or *anti*-**10** as major components. The synthesized functionalized amino esters are valuable intermediates, as demonstrated by the subsequent transformation of *anti*-**2** into the enantiopure building blocks **13**–**15**. Since precursor 1,2-oxazines were prepared via lithiated alkoxyallenes, the latter species were serving as formyl ester anion equivalents.

Introduction

We required enantiopure functionalized α-amino-β-hydroxy esters **A** in reasonable quantities for stereocontrolled syntheses of certain polyhydroxylated amines such as sphingosine or polyoxamic acid. Suitable precursors for these building blocks should be 1,2-oxazine derivatives **B**, smoothly available from the lithiated alkoxyallenes and carbohydrate-derived aldonitrones **C** (Scheme 1).[1] In this anticipated overall sequence, lithiated alkoxyallenes were again expected to serve as formyl ester anion equivalents[2] – a valuable synthetic application that we had already been able to establish via methoxyallene-amino aldehyde adducts, affording α-hydroxy-β-amino acid derivatives.[3] For the transformation **B** → **A** we planned an oxidative cleavage of the enol ether double bond of functionalized 1,2-oxazines **B**. A variety of other synthetically very useful compounds derived from heterocycles **B** were developed by our group; all these transformations, however, are based on reductive or acid-induced hydrolytic conditions.[4]



Scheme 1.

Results

Stereodivergent syntheses of the required *syn*- and *anti*-configured 1,2-oxazines **1**, **5**, **8** and **11** were recently described in full detail,[1] and most of the compounds are smoothly available in useful quantities. Since we assumed that the nucleophilicity of the benzyl-substituted nitrogen in the 1,2-oxazines may cause side reactions during ozonolysis, we first tried to perform the ozonolysis of *anti*-**1** in the presence of one equivalent of acid, which should block the nitrogen by protonation. These conditions provided unsatisfactory results, but instead it turned out that the reaction could be performed without any precautions. Ozonolysis of *syn*-**1** and *anti*-**1** at –78 °C in methanol, followed by in situ treatment with acetic anhydride and triethylamine at room temperature,[5] furnished the desired esters *syn*-**2** or *anti*-**2** in 60 % and 68 % yields. Interestingly, considerable amounts of the 5-hydroxy-substituted 1,2-oxazine ketals **3** were isolated in both reactions (Scheme 2). Formation of the desired esters **2** proceeds via the expected hydroperoxides **4**,[6a] which could be isolated and fully characterized when the second step of our standard procedure was omitted.

The mechanism transforming intermediates **4** into **2** by *O*-acylation and elimination−actually an internal redox process−is straightforward,[5] whereas the formation of 5-hydroxylated 1,2-oxazines **3** is less easy to explain[6] and will be discussed in a future full account.[7] At present we have to state that all attempts to decrease or increase the amount of these side products by modifying the reaction conditions had only limited success. Compounds such as *syn*-**3** and *anti*-**3** should be valuable intermediates for further synthetic endeavours employing functionalized 1,2-oxazines as stereodefined functionalized templates.[4]

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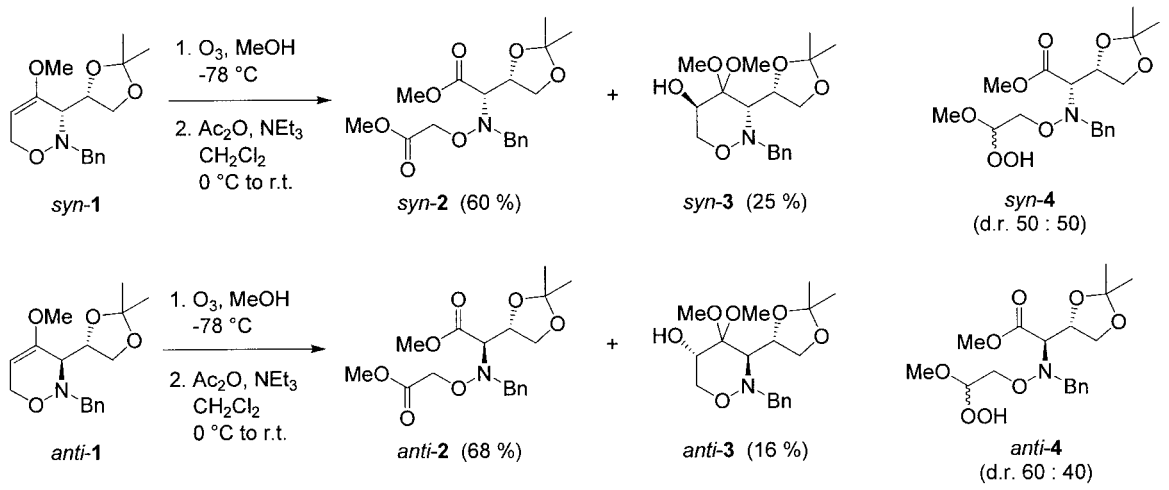
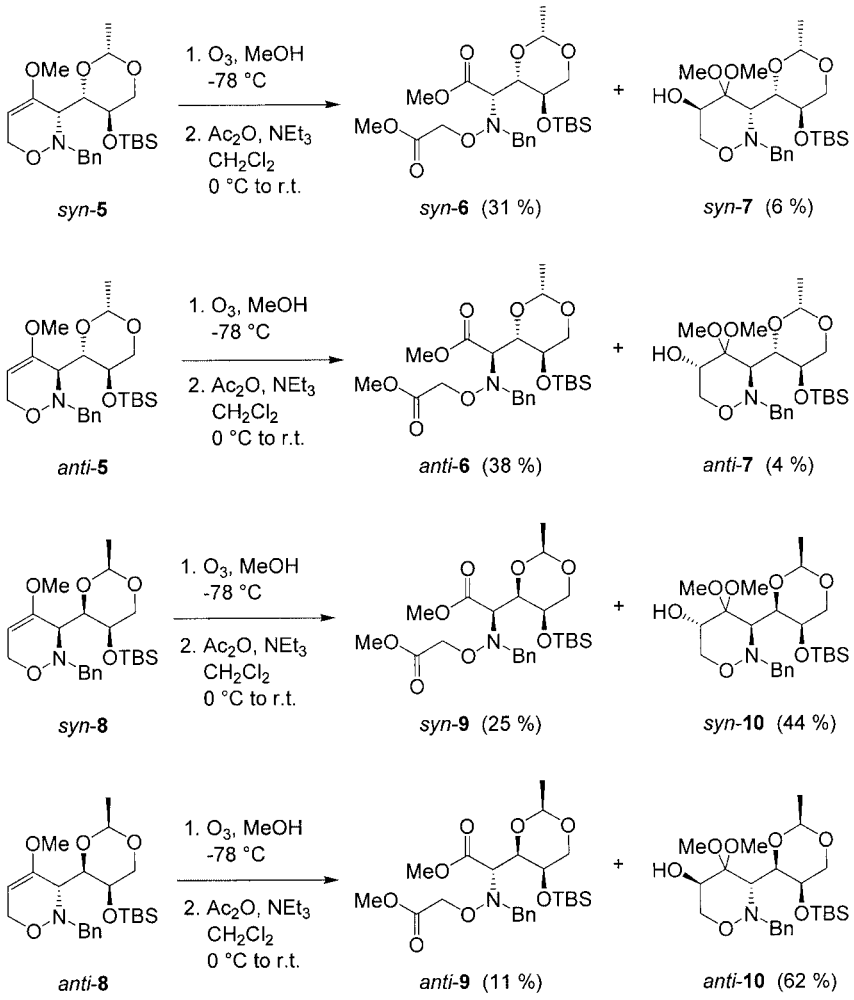


Scheme 2.

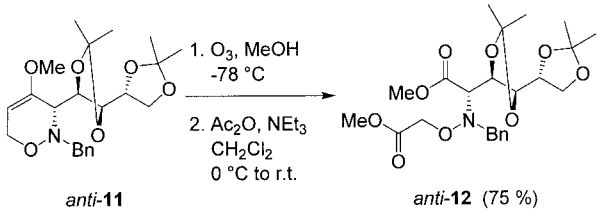
Similar observations were made with D-erythrose-derived *syn*-**5** and *anti*-**5**, which afforded the expected diastereomeric esters *syn*-**6** and *anti*-**6** in moderate yields, together with relatively small amounts of 5-hydroxylated 1,2-oxazines **7** (Scheme 3). Remarkably, the diastereomers *syn*-**8** and *anti*-**8**, both actually derived from D-threose, provided the 1,2-oxazine ketals *syn*-**10** and *anti*-**10** as major component, with the expected amino esters **9** being formed only in low yields. The preferred reaction pathway, involving either conventional fragmentation of the intermediate primary



Scheme 3.

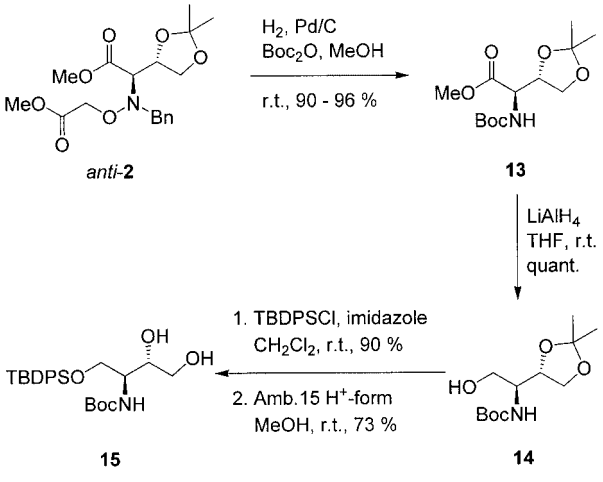
ozonide with cleavage of the enol ether double bond or the formation of the 5-hydroxylated 1,2-oxazines, is apparently strongly dependent on the configuration of the precursor compounds.

We also introduced the arabinose-derived *anti*-configured 1,2-oxazine **11** into the ozonolysis/elimination sequence and gratifyingly obtained the desired functionalized α-amino ester **12** in good yield (Scheme 4). No side-product was isolated in this reaction. All compounds isolated after the oxidative cleavage of the 1,2-oxazine ring still show the relative configurations of their starting materials. The amino group of the resulting amino esters is unusually protected by a (methoxycarbonyl)methoxy fragment. This hydroxylamine moiety is of course prone to reductive cleavage as shown below.



Scheme 4.

To demonstrate the synthetic value of functionalized and protected α-amino esters such as *anti*-**2** we disclose a few representative transformations of these compounds (Scheme 5). Palladium-catalyzed hydrogenolysis of *anti*-**2** in the presence of Boc-anhydride furnished the desired protected α-amino ester **13** in excellent yield. This compound could be further reduced with lithium aluminium hydride to produce alcohol **14**, which was converted into the selectively protected enantiopure aminotriol **15** by standard methods.



Scheme 5.

Conclusions

The reactions depicted in Schemes 2–4 reveal that lithiated methoxyallene efficiently serves as the desired formyl ester anion equivalent.[8] The involved formal Umpolung of reactivity is a special feature of many reactions of lithiated alkoxyallenes and strongly contributes to their synthetic value and high versatility.[9] Scheme 5 depicts some initial straightforward transformations of *anti*-**2**, showing its synthetic usefulness. Future reports will demonstrate that 5-hydroxy-substituted 1,2-oxazine derivatives such as *syn*-**10**, formed during the ozonolyses as minor or even as major components, may also be of preparative value. The ozonolyses[10] of enantiopure 1,2-oxazine derivatives is therefore a new and valuable tool for the conversion of these heterocycles into new highly functionalized products.

Experimental Section

For general information see ref.[1a] All new compounds displayed the expected analytical and spectroscopic data.

Typical Procedure for Ozonolysis: Conversion of *anti*-1 into *anti*-2 and *anti*-3: Argon was bubbled through a solution of 1,2-oxazine *anti*-**1** (1.00 g, 3.27 mmol) in methanol (150 mL) for 5 min with cooling to –78 °C. Ozone in oxygen was then introduced until the solution remained blue for 5 min, followed by oxygen for 15 min. The reaction mixture was allowed to warm to room temperature over 2 h and the solvent was evaporated at room temperature. The crude reaction mixture was dissolved in dichloromethane (30 mL), and acetic anhydride (2.5 mL, 2.67 g, 26.2 mmol) and triethylamine (0.9 mL, 0.66 g, 6.55 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then for 21 h at room temperature. After the addition of methanol (2.5 mL) the mixture was stirred for further 10 min, diethyl ether (90 mL) was then added, and the organic layer was extracted twice with sodium hydrogencarbonate solution (5 % in water, 40 mL) and once with water (40 mL). The organic phase was dried with magnesium sulfate and the solvent was evaporated to yield the crude product (1.30 g) as a colourless, viscous oil. Column chromatography (silica gel, hexane/ethyl acetate 3:1) gave *anti*-**2** (817 mg, 68 %) and *anti*-**3** (180 mg, 16 %) as colourless oils.

Compound *anti*-2: $[\alpha]_D^{22}$ = +28.1 (*c* = 0.96, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.27, 1.28 (2 × s, each 3 H, Me), 3.63, 3.77 (2 × s, each 3 H, OMe), 3.77–3.85 (m_c, 1 H, 2-H), 3.83 (dd, ^2J = 8.7, ^3J = 5.5 Hz, 1 H, 4-H_A), 3.88 (d, ^2J = 16.3 Hz, 1 H, 2′-H_A), 4.00 (dd, ^2J = 8.7, ^3J = 6.3 Hz, 1 H, 4-H_B), 4.01 (d, ^2J = 16.3 Hz, 1 H, 2′-H_B), 4.06, 4.15 (2 × d, ^2J = 13.2 Hz, each 1 H, C*H* $_2$Ph), 4.49 (m_c, 1 H, 3-H), 7.21–7.29 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 25.3, 26.6 (2 × q, Me), 51.7, 51.8 (2 × q, OMe), 60.0 (t, *C*H_2Ph), 67.2, (t, C-4), 70.0 (d, C-2), 71.9 (t, C-2′), 73.8 (d, C-3), 109.6 (s, *C*Me_2), 127.8, 128.4, 129.8, 136.5 (3 × d, s, Ph), 169.3, 169.9 (2 × s, C=O). IR (film): $\tilde{\nu}$ = 3090–3030 (=C-H), 2985–2840 (C-H), 1755 cm^{-1} (C=O). MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 367 (1) $[M]^+$, 178 (34), 101 (64) $[C_5H_9O_2]^+$, 91 (100) $[C_7H_7]^+$. HRMS (EI, 80 eV, 100 °C): calcd. for $C_{18}H_{25}NO_7$ 367.16310; found 367.16632. $C_{18}H_{25}NO_7$ (367.4): calcd. C 58.85, H 6.86, N 3.81; found C 58.70, H 6.86, N 3.61.

(3*R*,5*S*)-2-Benzyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-hydroxy-4,4-dimethoxy-3,4,5,6-tetrahydro-2*H*-[1,2]oxazine (*anti*-3): $[\alpha]_D^{22}$ = +31.9 (*c* = 1.59, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.45, 1.49 (2 × s, each 3 H, Me), 3.12 (s, 3 H, OMe), 3.14–3.16 (m, 1 H, 3-H), 3.34 (s, 3 H, OMe), 3.60 (bd, ^3J = 7.9 Hz, 1 H, 5-H), 3.80 (dt, ^2J = 12.0, ^3J = 1.1 Hz, 1 H, 6-H_A), 3.96 (d, ^2J = 13.6 Hz, 1 H, C*H* $_2$Ph), 4.01 (dd, ^2J = 8.0, ^3J = 6.6 Hz, 1 H, 5′-H_B), 4.22 (dd, ^2J = 12.0, ^3J = 2.1 Hz, 1 H, 6-H_B), 4.24 (dd, ^2J = 8.0, ^3J = 9.2 Hz, 1 H, 5′-H_B), 4.28 (d, ^2J = 13.6 Hz, 1 H, C*H* $_2$Ph), 4.69 (d, ^3J =

7.9 Hz, 1 H, OH), 4.77 (ddd, ^3J = 9.2, 6.6, 1.6 Hz, 1 H, 4′-H), 7.24–7.38 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 26.0 (q, 2 × Me), 47.6, 48.1 (2 × q, OMe), 57.7 (t, *C*H_2Ph), 60.1 (d, C-3), 66.8 (d, C-5), 68.0 (t, C-5′), 72.6 (t, C-6), 72.9 (d, C-4′), 99.6 (s, C-4), 109.7 (s, *C*Me_2), 127.3, 128.3, 128.6, 137.0 (3 × d, s, Ph). IR (film): $\tilde{\nu}$ = 3390 (OH), 3085–3030 (=C-H), 2985–2835 (C-H), 1605 cm^{-1} (C=C). MS (EI, 80 eV, 120 °C): *m*/*z* (%) = 353 (1) $[M]^+$, 253 (15), 252 (64) $[M - C_5H_9O_2]^+$, 104 (17), 101 (22) $[C_5H_9O_2]^+$, 91 (100) $[C_7H_7]^+$. HRMS (EI, 80 eV, 120 °C): calcd. for M^+ ($C_{18}H_{27}NO_6$): 353.18384, found: 353.18567. $C_{18}H_{25}NO_6$ (353.4): calcd. C 61.17, H 7.70, N 3.96; found C 61.24, H 7.68, N 3.76.

Acknowledgments

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[7] The configurations of *syn*-**3** and *anti*-**3** as depicted in Scheme 2 were confirmed by NOESY experiments and are the result of ozone attack *trans* with regard to the dioxolane rings of the starting materials *syn*-**1** and *anti*-**1**.

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[10] Other methods for oxidative cleavage of the enol ether double bond of 1,2-oxazines such as *anti*-**1** have not yet been successful; either no reaction occurred or very complex product mixtures were obtained; M. Helms, unpublished results.

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