Ring Enlargement of Enantiopure 1,2-Oxazines to 1,2-Oxazepine Derivatives and Their Palladium-Catalyzed Couplings

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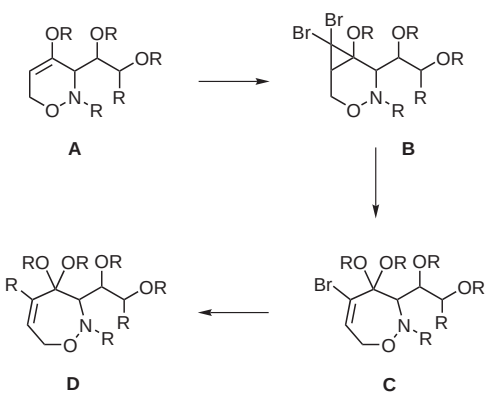
Abstract: Phase-transfer-catalyzed cyclopropanation of enantiopure 1,2-oxazine derivatives *anti*-**1a**,**b** or *syn*-**1** followed by solvolysis of the resulting geminal dibromocyclopropane intermediates afforded the expected ring-expanded products, namely 1,2-oxazepines *anti*-**3a**,**b** or *syn*-**3**. These heterocycles could be further substituted by use of their bromoalkenyl group employing palladium-catalyzed coupling reactions, which smoothly led to new enantiopure 1,2-oxazepine derivatives *anti*-**4**–*anti*-**8**.

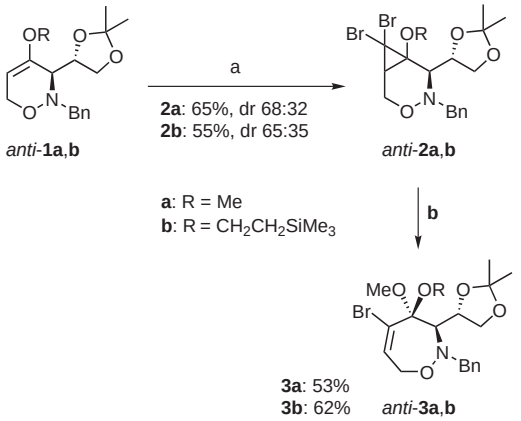
Key words: dibromocyclopropanes, ring enlargement, 1,2-oxazines, 1,2-oxazepines, palladium catalysis

We have recently demonstrated that readily available 3,6-dihydro-2*H*-1,2-oxazines **A**[1] are versatile intermediates for syntheses of several classes of enantiopure compounds.[2] Here we enclose that homologous compounds **C** are smoothly available via intermediate geminal dibromocyclopropanes **B**. The palladium-catalyzed coupling reactions of bromoalkenes **C** led to new 1,2-oxazepines **D** of considerable diversity (Scheme 1).



Scheme 1 Transformation of 3,6-dihydro-2*H*-1,2-oxazines **A** into enantiopure 1,2-oxazepine derivatives **C** and **D** via dibromocyclopropanes **B**.

Enantiopure 1,2-oxazines *anti*-**1a**,**b** were first treated with bromoform, potassium fluoride, and sodium hydroxide in the presence of a phase transfer catalyst, which furnished the desired dibromocyclopropane derivatives *anti*-**2a**,**b** in moderate yields with low diastereoselectivities (Scheme 2). It is noteworthy that experiments which were carried out using bromoform and base but without addition of potassium fluoride did not lead to *anti*-**2a**,**b**. Instead, the starting material underwent fast decomposition. This problem has, however, been circumvented by employing a large excess of potassium fluoride. Similar observations have been described in literature for related reactions.[3] Subsequent solvolysis of the dibromocyclopropane derivatives in refluxing methanol with potassium carbonate[3] gave the expected 1,2-oxazepine derivatives *anti*-**3a**,**b** in moderate yields. The isolation of 1,2-oxazepine derivative *anti*-**3b** as a single diastereomer can be attributed to the fact that the intermediate allylic cation probably accepts the nucleophile methanol with high preference *trans* to the bulky dioxolanyl group.



Scheme 2 *Reagents and conditions*: a) $CHBr_3$, 50% NaOH (aq), KF, Et_3BnNCl, r.t., 2 d; b) K_2CO_3, MeOH, reflux, 20 h.

The diastereomeric enantiopure 3,6-dihydro-2*H*-1,2-oxazine *syn*-**1** was analogously converted into the ring-expanded heterocycle *syn*-**3** in moderate overall yield (Scheme 3).[4] The geminal dibromocyclopropane derivatives **2** could be isolated (and the diastereomers may be separated) but in general it is more efficient to use unseparated intermediates **2** for the solvolysis reactions leading to 1,2-oxazepines **3**.

Enantiopure seven-membered 1,2-oxazepines[5] *anti*-**3a**,**b** and *syn*-**3** allow an approach to many interesting product classes, e.g. amino-substituted polyols (heptanose derivatives) or stereodefined enantiopure piperidines. As well, the presence of a bromoalkenyl moiety makes these 1,2-oxazepine derivatives ideal candidates for palladium-catalyzed coupling reactions. Scheme 4 summarizes our preliminary results employing *anti*-**3a**, which demon-

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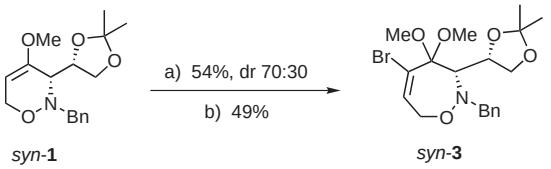
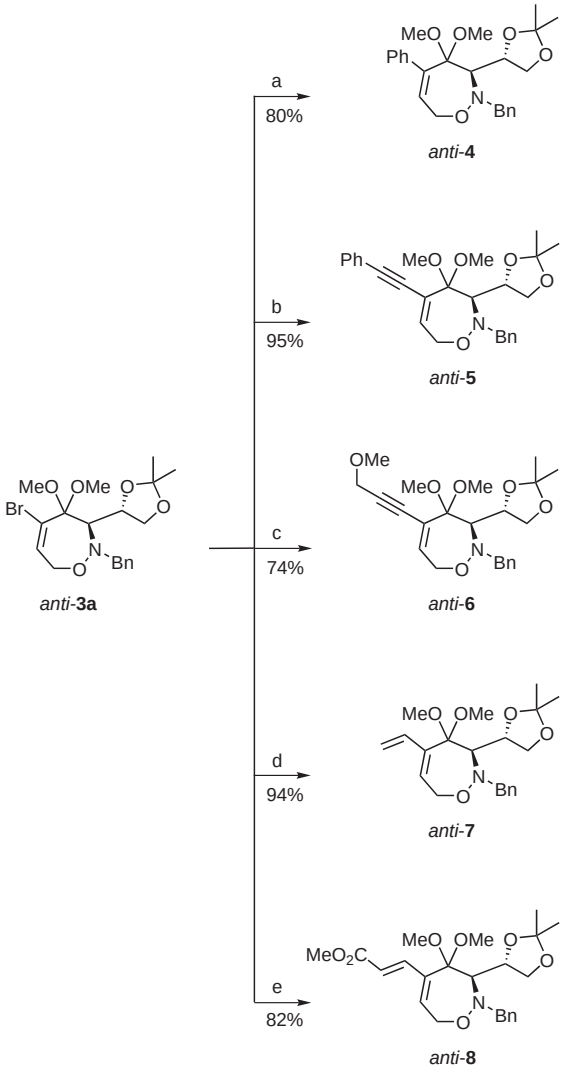


Scheme 3 *Reagents and conditions*: a) $CHBr_3$, 50% NaOH (aq), KF, Et_3BnNCl, r.t., 2 d; b) K_2CO_3, MeOH, reflux, 20 h.

strate that Suzuki couplings[6] or Sonogashira reactions[7] provide compounds such as *anti*-**4**, *anti*-**5**, and *anti*-**6**, respectively, in excellent yields. Gratifyingly, Stille reactions[8] and Heck couplings[9] of 1,2-oxazepine *anti*-**3a** also occurred smoothly delivering 1,3-dienes *anti*-**7** and *anti*-**8** with very good efficacy. These latter coupling products should be excellent partners in Diels–Alder reactions, which may lead to interesting enantiopure skeletons incorporating a 1,2-oxazepine ring.



Scheme 4 *Reagents and conditions*: a) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 70 °C, 10 h; b) phenylacetylene, $Pd(OAc)_2$, PPh_3, CuI, *i*-Pr_2NH, DMF, r.t., 10 h; c) 3-methoxypropyne, $Pd(OAc)_2$, PPh_3, CuI, *i*-Pr_2NH, DMF, r.t., 10 h; d) tributylvinylstannane, $Pd(OAc)_2$, PPh_3, DMF, 65 °C, 3 h; e) methyl acrylate, $Pd(OAc)_2$, LiCl, Et_3N, DMF, 70 °C, 10 h.

In conclusion, the cyclopropanation–ring enlargement sequence of enantiopure 1,2-oxazines leads to homologous 1,2-oxazepine derivatives, which should have a high potential for diversity orientated chemistry.[10]

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(4) **Typical Procedure, conversion of *anti*-1a into *anti*-3a.** A solution of NaOH (0.60 g) and KF (4.10 g) in H_2O (4.10 mL) was added to a vigorously stirred solution of *anti*-**1a** (0.50 g, 1.64 mmol) in $CHBr_3$ (2.70 mL) containing benzyltriethylammonium chloride (5.5 mg). The biphasic mixture was stirred for 2 d at r.t. and then diluted with H_2O (8 mL) and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried (Na_2SO_4) and concentrated. The excess $CHBr_3$ was removed in vacuum. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 4:1) to give **2a** as colorless liquid (511 mg, 65%, dr 68:32).
Dibromocyclopropane derivative **2a** was refluxed for 20 h in a solution of anhyd K_2CO_3 (0.87 g, 6.27 mmol) in MeOH (7 mL) under Ar atmosphere. The mixture was cooled to r.t., diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to yield 241 mg (53%) of *anti*-**3a** as colorless oil.
Analytical data for (3*R*,4′*S*)-2-benzyl-5-bromo-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4,4-dimethoxy-2,3,4,7-tetrahydro-1,2-oxazepine: $[\alpha]_D^{22}$ –84.2 (*c* 0.45, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.33, 1.36 (2 s, 3 H each, Me), 3.19, 3.29 (2 s, 3 H each, OMe), 3.28 (d, *J* = 5.6 Hz, 1 H, 3-H), 4.07 (dd, *J* = 8.4, 8.8 Hz, 1 H, 5′-H), 4.11 (dd, *J* = 8.0, 8.4 Hz, 1 H, 5′-H), 4.29, 4.34 (2 d, *J* = 14.0 Hz, 1 H each,

NCH_2), 4.31 (m_c, 1 H, 4′-H), 4.37 (dd, *J* = 1.1, 13.5 Hz, 1 H, 7-H), 4.47 (dd, *J* = 0.8, 13.5 Hz, 1 H, 7-H), 6.70 (dd, *J* = 0.8, 1.1 Hz, 1 H, 6-H), 7.24–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.7, 26.3 (2 q, CH_3), 49.0, 49.1 (2 q, OMe), 58.1 (t, NCH_2), 63.6 (t, C-7), 66.7 (d, C-3), 67.2 (t, C-5′), 74.9 (d, C-4′), 99.2 (d, C-2′), 108.5 (d, C-6), 108.9 (s, C-4), 127.1, 128.2, 128.6, 138.0 (3 d, s, Ph), 135.3 (s, C-5) ppm. IR (KBr): ν = 3090–3030 (=C–H), 2985–2845 (C–H), 1635 (C=C) cm^{-1}. MS (EI, 80 eV, 100 °C): *m/z* (%) = 429 (1) $[M]^+$, 427 (1) $[M]^+$, 414 (1) $[M - CH_3]^+$, 412 (1) $[M - CH_3]^+$, 398 (0.4) $[M - OCH_3]^+$, 396 (0.4) $[M - OCH_3]^+$, 329 (6) $[M - CH_5H_9O_2]^+$, 327 (6) $[M - CH_5H_9O_2]^+$, 91 (100) $[CH_2Ph]^+$. Anal. Calcd for $C_{19}H_{20}BrNO_5$ (428.3): C, 53.28; H, 6.12; N, 3.27. Found: C, 53.10; H, 5.91; N, 2.68. HRMS (EI, 80 eV, 100 °C): *m/z* calcd for $C_{19}H_{20}{}^{79}BrNO_5$: 427.09943; found: 427.09947; *m/z* calcd for $C_{19}H_{20}{}^{81}BrNO_5$: 429.09744; found: 429.09738.

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