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Sequential ring-opening of *trans*-1,4-cyclohexadiene dioxide for an expedient modular approach to 6,7-disubstituted (±)-hexahydro-benzo[1,4]oxazin-3-ones

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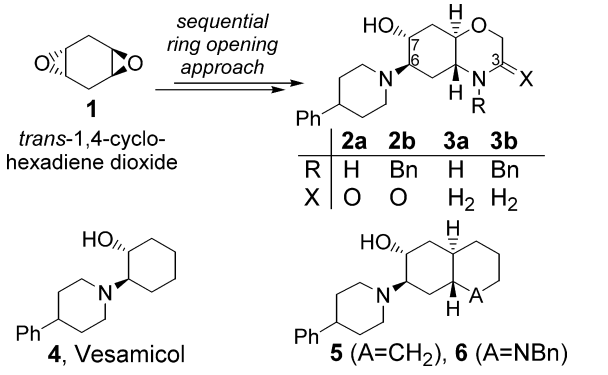
Abstract—A modular approach to novel 6-amino-7-hydroxysubstituted hexahydro-benzo[1,4]oxazin-3-ones has been developed. The method involves a sequential ring-opening of *trans*-1,4-cyclohexadiene dioxide with amino nucleophiles. The resultant mono-epoxide from benzylamine was converted to a general electrophilic precursor, which enables the parallel treatment with amino nucleophiles to obtain a series of cyclohexane-fused morpholin-3-ones.

The ring-cleavage of strained heterocyclic electrophiles has been evaluated as one of the few reliable conversions for the assembly of variable structures via heteroatom–carbon bonds in 'click'-chemistry.[1] Surprisingly, symmetric diepoxides have scarcely been used for sequential opening with not identical heteroatom nucleophiles,[2] in contrast to concurrent diepoxide ring-opening applying a single nucleophile.[1a] Until now, only *trans*-cyclopenta-1,3-diene dioxide was regarded for an intermolecular reaction sequence with varying amines.[3] In the search for a new approach to variously substituted cyclohexane-fused morpholin-3-ones (**2a** and **2b**, Scheme 1), we attempted to take advantage of sequentially attacking the two electrophilic sites of *trans*-1,4-cyclohexadiene dioxide (**1**) by two different amines. The morpholin-3-one motif, found in only a few natural products,[4] is quested as valuable intermediate for numerous conversions.[5] By comparison, cyclohexane-fused morpholin-3-ones (hexahydro-benzo[1,4]oxazin-3-ones) were also frequently processed in reactions such as ring-opening,[6] annulation,[7] or reduction.[8]



Scheme 1.

The latter scaffold resembles closely to the decahydro-naphthalene and decahydro-quinoline substructure. Both have been used as constituents of conformationally fixed analogues of vesamicol (Scheme 1, **4**), which is the parent structure of numerous ligands for the vesicular acetylcholine transporter (VAChT).[9] The VAChT is esteemed as a favourable target to detect pathological alterations of cholinergic terminals by PET (positron emission tomography).[10] Derivatives consisting of a

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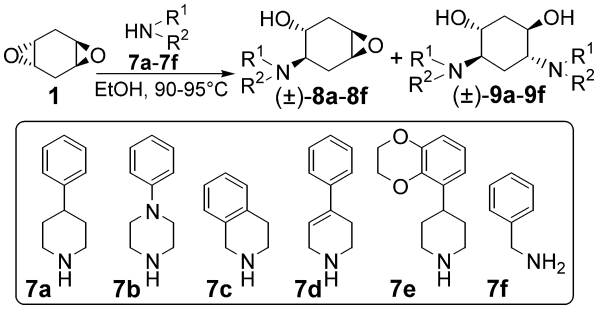


Scheme 2.

bicyclic skeleton, such as **5**[11] and **6**,[12] have been communicated as highly potent VAChT ligands. In the continuous search for new VAChT ligands with improved binding profiles,[13] we were interested in structures such as **2a**,**b** and **3a**,**b** as rigid analogues of **4**. In this Letter, we describe the synthesis of different 6-amino-7-hydroxysubstituted hexahydro-benzo[1,4]oxazin-3-ones using the sequential ring-opening of *trans*-1,4-cyclohexadiene dioxide as a key step. The required diepoxide **1** was prepared from cyclohexa-1,4-diene by applying the well-tried combination of methyltrioxorhenium (MTO)/hydrogen peroxide (H_2O_2) with pyridine as additive.[14] An experiment for the partial cleavage of **1** at the outset of our study is depicted in Scheme 2.

The treatment of 4-phenyl-piperidine (**7a**) with a two-fold excess (200 mol %) of *trans*-1,4-cyclohexadiene dioxide (**1**) in EtOH at 90–95 °C for 16 h in a closed vessel led to the desired mono-epoxide **8a** in 75% yield and **9a**, which was isolated in 12% yield.[15,16] Further investigations towards product distribution and efficiency of conversions were carried out with a series of secondary amines (**7a**–**e**) and benzylamine (**7f**). The results are summarized in Table 1.

The application of 100 mol % **1** in relation to **7a** led to **8a** in 36% yield (Table 1, entry 2), which, in contrast to entry 1, clearly demonstrated the necessity to use an overstoichiometric amount of the diepoxide. As expected, a decrease of **1** to 50 mol % resulted in **9a** as the single product (Table 1, entry 3). In experiments of **1** with a couple of other secondary amines, it has been shown to be beneficial to raise the molar ratio from 2:1 to 5:1 (Table 1, entry 4 vs 6, 7 vs 8, 9 vs 10). Both selectivity and yield were positively affected by increasing the amount of **1** to 500 mol %. In addition, the reaction time sufficient for the total conversion of the amine was reduced to 1 h (Table 1, entries 6, 10 and 11). Somewhat longer reaction times were needed for the conversion of benzylic amines **7c** and **7f** (Table 1, entries 8 and 12). The bulk of unreacted *trans*-1,4-cyclohexadiene dioxide (**1**) could be readily recovered by applying a simple extraction procedure during work-up. It should be noted that all diols isolated (**9a**–**d**) were proven to result from a second nucleophilic cleavage on the 3-position in relation to the position of the primarily attacking nucleophile.[17] The appearance of four individual ^{13}C-signals for the cyclohexane moiety corresponds to a molecule with C_2-symmetry.[18] This was expected and is in accordance to the known *trans*-diaxial selectivity of nucleophilic cleavages on **1**.[1a,18,19]

Table 1. Products from the reaction of **1** with amines **7a**–**f** (Scheme 2)[a]

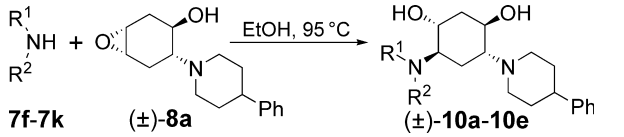
Entry	Reactants		Time (h)	Isolated products			
	Amine	**1**[b] (mol %)		No.	Yield[c] (%)	No.	Yield[c] (%)
1	**7a**	200	16	**8a**	75 (68)	**9a**	12
2	**7a**	100	22	**8a**	36	**9a**	34
3	**7a**	50	72	—	—[d]	**9a**	78
4	**7b**	200	13	**8b**	70 (42)	**9b**	15
5	**7b**	300	5	**8b**	75 (43)	**9b**	9
6	**7b**	500	1	**8b**	83 (71)	**9b**	5
7	**7c**	200	12	**8c**	52 (15)	**9c**	12
8	**7c**	500	1.5	**8c**	76 (61)	**9c**	5
9	**7d**	200	5	**8d**	53 (32)	**9d**	11
10	**7d**	500	1	**8d**	79 (70)	**9d**	4
11	**7e**	500	1	**8e**	72	—	[d]
12	**7f**	500	2.5	**8f**	60 (52)	—	[d]

[a] Reaction conditions: **1** in EtOH [~1.25 M], entry 3: **1** in EtOH [~0.62 M], amine [**7a**–**f**, 0.2–2 equiv], stirring in a closed vessel at 95 °C; all products are racemic, the formulae represent *relative* configurations.
[b] Surplus of **1** was recovered in yields of 90–99%.[15]
[c] Overall yields of isolated products after chromatographic purification; yields in parenthesis refer to crystallized products, after removal of **1**; **8a**–**f**, **9a**–**d** are new compounds and were fully characterized.
[d] Compound **8a** was not observed; diols **9e** and **9f** were not isolated.

Having in hands electrophilic 4-amino-7-oxa-bicyclo-[4.1.0]heptan-3-ols (**8a**–**f**), we turned our interest to the modular synthesis of non-symmetrical 4,6-di-amino cyclohexane-1,3-diols starting from **8a**.

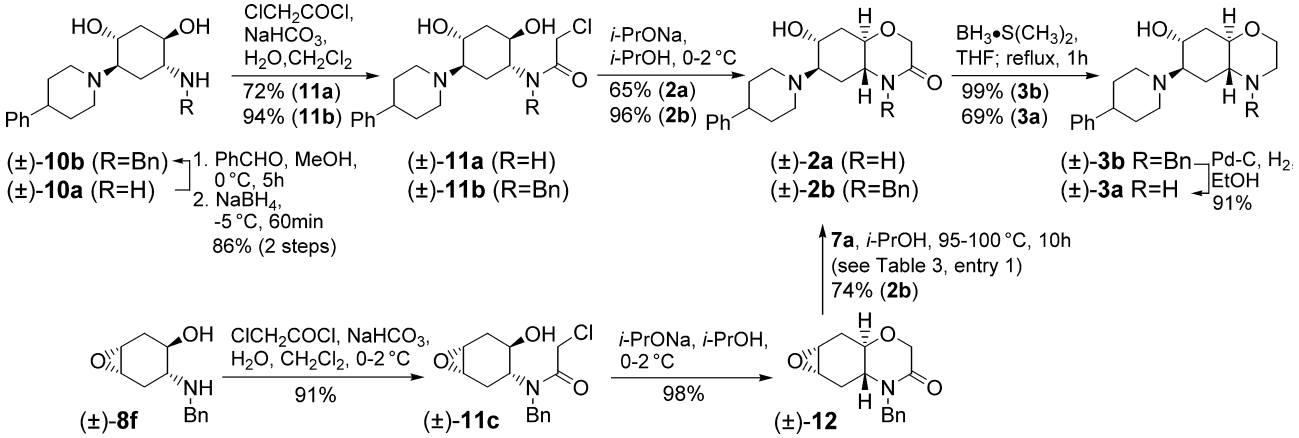
As outlined in Table 2, the attack of **7f** or **7g** on **8a** led with high regio- and stereoselectivity to compounds **10b** and **10c** (Table 2, entries 2 and 3). However, crystalline products were obtained only in moderate yields. In comparison, smaller and more nucleophilic amines (**7h**,**i**,**k**),

Table 2. Amino-6-(4-phenyl-piperidin-1-yl)-cyclohexane-1,3-diols (**10a**–**e**) from the reaction of **8a** with amines[a]



Entry	Amine		Ratio **7**/**8a**	Time (h)	Product	
					No.	Yield[b] (%)
1	NH_3	**7h**	65	10	**10a**	99
2	$BnNH_2$	**7f**	6	16	**10b**	54
3	$4\text{-}FBnNH_2$	**7g**	4	8	**10c**	72
4	$HOC_2H_4NH_2$	**7i**	10	10	**10d**	96
5	HOC_2H_4NHMe	**7k**	4	13	**10e**	85

[a] Reaction conditions: **8a** in EtOH [~1.0 M], amine [**7f**–**g**, **7i**–**k**, 4–10 equiv], stirring in a closed vessel at 95 °C; entry 1: **7h** [30% w/w in H_2O, 65 equiv], stirring at 85–90 °C; all products are racemic, the formulae represent *relative* configurations.
[b] Yields of isolated products; **10a**–**e** are new compounds and were fully characterized.



Scheme 3.

which were applied in molar ratios of 4–10 (65 for ammonia, **7h**), led to the expected products from a *trans*-diaxial attack in excellent yields (Table 2, entries 1, 4 and 5).[20]

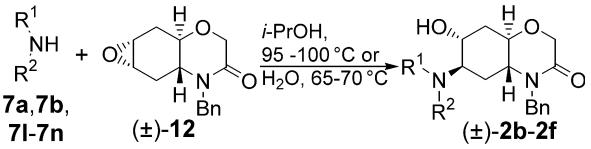
In a preliminary attempt to obtain 6,7-disubstituted hexahydro-benzo[1,4]oxazin-3-ones, the *N*-benzylamine derivative **10b** was needed and it was appropriately synthesized by a reductive benzylation of **10a** (Scheme 3). This procedure displayed an overall yield of 85% for three steps, which is in contrast to the only moderate yield of **10b** obtained in direct synthesis from **8a** and benzylamine (**7f**, Table 2, entry 2).

A standard sequence was applied to synthesize hexahydro-benzo[1,4]oxazin-3-ones **2a** and **2b** (Scheme 3). *N*-Chloroacetylation of **10a** and **10b** was carried out according to Schotten–Baumann conditions. For the ring closure of **11a** and **11b**, working in a solution of sodium *iso*-propanolate in *iso*-propanol (*i*-PrOH) has been found to yield **2a** and **2b** in 65% and 96%, respectively.

In order to achieve a superior access to **2b**, which might allow a parallel processing of a series of diverse amines, a general precursor **12** was conceived and prepared in two steps from **8f** (Scheme 3).

Epoxide **12** proved to be very useful as exemplified in a number of conversions with primary and secondary amines. The results are summarized in Table 3. In addition to experiments performed in *i*-PrOH at 95–100 °C, we also tested water as a reaction medium at 65–70 °C (Table 3, entries 2 and 7). Regarding reaction time and molar ratio of reactants, the most striking solvent effect was disclosed in the reaction with the bulky primary amine **7n**. Generally, reactions in water occurred faster (Table 3, entry 1 vs 2, entry 6 vs 7) and at a smaller amount of amine. However, the yields of **2b** and **2f** did not differ significantly from reactions proceeded in *i*-PrOH. Both products from the reaction of **7a** (Table 3, entries 1 and 2) were found to be identical with compound **2b** prepared via the aforementioned sequence starting from **10a** (Scheme 3). This outcome reempha-

Table 3. Formation of hexahydro-benzo[1,4]oxazin-3-ones (**2b–f**)[a]



Entry	Amine		Ratio **7**/**12**	Time (h)	Solv.	Product	
						No.	Yield[b] (%)
1	4-Phenyl-piperidine	**7a**	1.04	10	*i*-PrOH	**2b**	74
2	4-Phenyl-piperidine	**7a**	1.00	2	H_2O	**2b**	77
3	4-Phenyl-piperazine	**7b**	1.04	9	*i*-PrOH	**2c**	93
4	Pyrrolidine	**7l**	1.60	5	*i*-PrOH	**2d**	83
5	Piperidine	**7m**	1.60	7	*i*-PrOH	**2e**	76
6	*tert*-Butylamine	**7n**	20.0	96	*i*-PrOH	**2f**	83
7	*tert*-Butylamine	**7n**	2.00	15	H_2O	**2f**	75

[a] Reaction conditions: Entries 1, 3–6: **12** in *i*-PrOH [~1.25 M], amine [**7a**,**b**,**l**–**n**; 1.04–20 equiv], stirring in a closed vessel at 95–100 °C; Entries 2 and 7: **12** [1 equiv], H_2O [~100 equiv], amine [**7a**,**n**; 1–2 equiv], stirring at 65–70 °C; all products are racemic, the formulae represent *relative* configurations.

[b] Yields of isolated crystallized products; **2b**–**f** are new compounds and were fully characterized.

sized the mode of regioselectivity of aminolytic cleavages on substituted epoxides, such as **8a** and **12**.

Finally, we performed the conversion of **2a** and **2b** to the novel octahydro-benzo[1,4]oxazines **3a** and **3b**, respectively (Scheme 3). The reductions were carried out using borane dimethylsulfide complex in refluxing tetrahydrofurane. Secondary amine **3a**[21] was also accessible via debenzylation of **3b**. All new compounds were analyzed by ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry (TOF-MS, electrospray) confirming the proposed structures.

In conclusion, we developed an efficient procedure to attain partial aminolyses of *trans*-1,4-cyclohexadiene dioxide (**1**) with a range of different amines leading to reactive mono-epoxides (**8a–f**). Starting from **8a** we have diastereoselectively synthesized novel octahydro-benzo[1,4]oxazines (**3a**,**b**) via four steps. A general precursor, **12**, was prepared from **8f** and utilized for a straight approach to a series of diverse hexahydro-benzo[1,4]oxazin-3-ones (**2b–f**). Further investigations towards the enantiomerically pure synthesis of hexahydro-benzo[1,4]oxazin-3-ones are now in progress and will be published in a forthcoming paper.

Acknowledgement

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15. *Preparation of* (±)-**8a** *via partial ring-opening of* **1**: A mixture of **7a** (2.59 g, 16.05 mmol) and **1** (3.6 g, 32.1 mmol) in ethanol (20 mL) was stirred in a closed thick-walled glass flask for 16 h at 95 °C. After cooling, the crystalline precipitate was filtered off, washed with cold ethanol, and dried to give **8a** (2.98 g, 68%). After evaporation, the residue was treated with a mixture of citric acid (25%, 2.5 mL) and methyl *tert*-butyl ether (MTBE, 15 mL), and allowed to stir for 10 min. The organic layer was separated and the aqueous layer was extracted with MTBE (6 × 3 mL). The combined organic fractions were dried (Na_2CO_3), filtered, and concentrated to afford the bulk of unreacted **1** (1.69 g, 94% recovery) as off-white crystalline solid in pure form, which could be utilized again. The aqueous layer was made alkaline with 10% K_2CO_3. A sticky material precipitated, which was extracted with methylene chloride (CH_2Cl_2, 3 × 4 mL). The combined organic fractions were collected and concentrated. The residue was purified by flash column chromatography on silica gel 60 (CH_2Cl_2, MeOH, NH_4OH [30% in H_2O]; 10:1:0.1) to afford the remainder of **8a** (310 mg, 7%) and diol **9a** (417 mg, 12%).
16. *Analytical data for* (±)-**8a** *as selected compound*: White solid; mp 152–154 °C (ethanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60–1.72 (m, 2H), 1.79 (ddd, 1H, $J = 12$, 12, 4.8 Hz), 1.85–1.90 (m, 2H), 1.98 (dd, 1H, $J = 14.8$, 12 Hz), 2.10–2.18 (m, 1H), 2.25 (dt-like, 1H, $J = 11.4$, 2.4 Hz), 2.38–2.53 (m, 2H), 2.68–2.82 (m, 4H), 3.18–3.21 (m, 2H), 3.61 (dt-like, 1H, $J = 10$, 5.2 Hz), 3.98 (br s, 1H), 7.18–7.22 (m, 3H), 7.29–7.32 (m, 2H); ^{13}C NMR (100.567 MHz, $CDCl_3$): δ_C 20.87, 33.05, 33.70, 34.21, 42.72, 44.77, 51.43, 53.03, 53.33, 62.69, 65.36, 126.17, 126.72, 128.38, 145.92.; MS (ESI) m/z 274.2 [$(M+H)^+$]; Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.99; H, 8.80; N, 5.16.
17. *Analytical data for* (±)-**9a**: White solid; mp 148.5–150 °C (ethyl acetate/*n*-hexane, 1:4); ^{1}H NMR (200.140 MHz, $CDCl_3$): δ_H 1.59–1.94 (m, 10H, 5-H_2, Pip: 2 × 3′-H_2, 2 × 5′-H_2), 2.02 (t-like, $J = 5.9$ Hz, 2H, 2-H_2), 2.06–2.20 (m, 2H, Pip: 2 × 2′-H_b), 2.31–2.64 (m, 6H, 4-H, 6-H, Pip: 2 × 4′-H, 2 × 6′-H_b), 2.78 (br, 2H, 2 × OH), 2.90–3.02, 3.05–3.15 (2m, 4H, Pip: 2 × 4′-H, Pip: 2 × 2′-H_a, 2 × 6′-H_a), 4.08 (dt-like, $J = 5.9$, 5.9 Hz, 2H, 1-H, 3-H), 7.15–7.35 (m, 10H, ArH). ^{13}C NMR (50.325 MHz, $CDCl_3$): δ_C 18.84 (1C, 5-C), 33.96 (2C, Pip: 2 × 3′C), 34.18 (2C, Pip: 2 × 5′C), 35.38 (1C, 2-C), 43.04 (2C, Pip: 2 × 4′-C), 47.90 (2C, Pip: 2 × 2′C), 52.97 (2C, Pip: 2 × 6′C), 64.54 (2C, 4-C, 6-C), 65.94 (2C, 1-C, 3-C), 126.28 (2C_{Ar}, 2 × 4″-C), 126.94 (4C_{Ar}), 128.54 (4C_{Ar}), 146.43 (2C_{Ar}, 2 × 1″-C); MS (ESI)

m/*z* 435.3 [(M+H)$^+$]; Anal. Calcd for $C_{28}H_{38}N_2O_2$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.00; H, 8.82; N, 6.47.

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21. *Selected physical data for compound* (±)-**3a**: White solid; mp 218.5–219.5 °C ($CHCl_3$/methyl *tert*-butylether); ^{1}H NMR (300 MHz, DMSO-d_6/$CDCl_3$): δ 1.50–2.10 (m, 10H), 2.20 (br s, 1H), 2.28–2.48 (m, 2H), 2.59–2.80 (m, 2H), 2.87–3.13 (m, 3H), 3.28–3.42 (m, 2H), 3.50–3.56 (m, 1H), 3.73–3.79 (m, 1H), 4.14 (br s, 1H), 7.08–7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 33.3, 33.68, 33.74, 42.7, 46.6, 50.2, 52.3, 54.6, 64.2, 66.9, 68.4, 77.6, 125.9, 126.7, 128.2, 146.4; MS (ESI) *m*/*z* 317.2 [(M+H)$^+$].