Synthetic Methods

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Nucleophilic Opening of Oxabicyclic Ring Systems**

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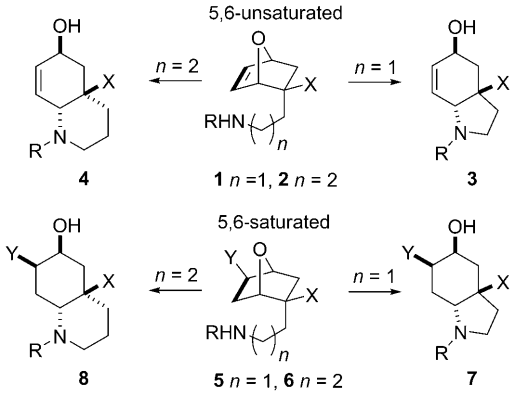
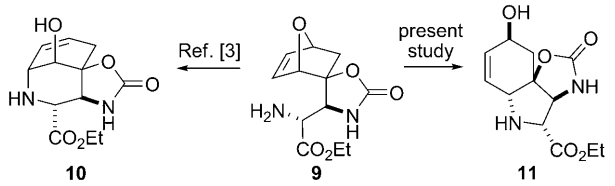
The ease of access to functionalized oxabicyclic ring systems renders them attractive starting points for chemical synthesis.[1] Their strategic incorporation in a synthesis can lead to considerable simplification of the route to a given target and provide key building blocks for asymmetric synthesis. In the context of our recent studies aimed at the synthesis of the banyaside and suomilide core structures,[2,3] we noted an unexpected transformation involving the opening of an oxabicyclo[2.2.1]heptene intermediate. Further investigations led us to identify unprecedented reactivity of oxabicyclic rings (Scheme 1). Herein, we document that oxabicyclo-



Scheme 1. Ring-opening reaction leading to hexahydroindoles **3** and octahydroquinolines **4**, as well as perhydroindoles **7** and perhydroiquinolines **8**.

[2.2.1]heptenes **1** and **2** are converted into hexahydroindoles **3** and octahydroquinolines **4**, respectively, in 50–95% yield upon treatment with $TMSOTf/NEt_3$. Astonishingly, the ring opening of saturated oxabicyclo[2.2.1]heptanes **5** and **6** (Y = H or OH) took place with equal ease. This unusual reactivity opens up rapid access to functionalized reduced indoles and quinolines.

In the course of our synthetic efforts towards the total synthesis of banyasides A and B and suomilide, we used an oxabicyclo[2.2.1]heptene in the rapid assembly of the common stereochemically complex core. In the reported strategy, the intramolecular olefin amination of **9** was followed by remote C–O bond cleavage to give **10** (Scheme 2), a process which may be described formally as



Scheme 2. Strategies for the cleavage of oxabicyclo[2.2.1]heptenes.

an allylic displacement reaction. The precursor oxabicyclo-[2.2.1]heptene **9** proved to be readily accessible through the implementation of a tandem Diels–Alder/aldol sequence.[4] In the course of these studies, we explored numerous methods for the direct conversion of **9** into **10**. One particular line of investigation included the examination of Rh^I catalysis. This approach was inspired by studies by Lautens and co-workers, who pioneered the use of metal catalysts and reagents for the opening of oxabicyclic rings.[5,6] In initial experiments, we observed that the treatment of **9** with a catalyst formed by the combination of (*R*,*S*)-josiphos with Rh^I in the presence of AgOTf and Bu_4NI afforded the tricyclic product **11** in 65% yield. Although **11** was an undesired product, we proceeded to examine this transformation further, as it had not been documented previously. Moreover, rhodium-mediated product formation was unexpected on the basis of observations with and the mechanistic constructs suggested for related systems.[7]

Additional studies of the conversion of oxabicyclo-[2.2.1]heptene **9** into **11** proved revealing (Table 1). The use of the cationic catalyst $[Rh(cod)_2OTf]$[8] led to the isolation of **11** in slightly improved yield (67%) and to the hypothesis that the Rh complex might be functioning as an electrophilic activator. Consequently, we screened a number of Lewis acids, including $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $MgBr_2$, BBr_3, and silyl triflates; only BBr_3 and the silyl triflates gave leading results.

The treatment of **9** with BBr_3 furnished **11** in 20% yield. By contrast, the exposure of **9** to $TMSOTf/Et_3N$ afforded **11** in 95% yield. When the more hindered *tert*-butyldimethylsilyl triflate was employed, some conversion was observed, but at a considerably reduced rate, to give the product in 36% yield. Interestingly, the use of a mixture of $TfOH/NEt_3$ did not lead

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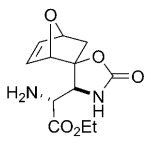
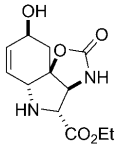
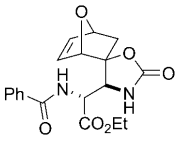
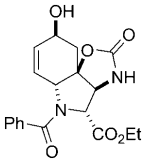
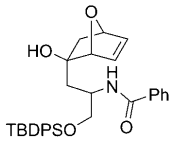
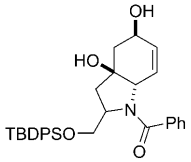
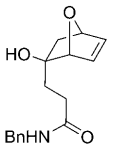
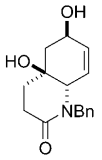
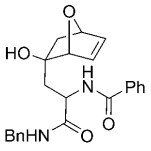
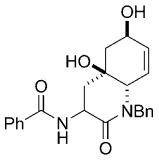
Table 1: Screening of reaction conditions for the conversion of **9** into **11**.

Entry	Conditions	Yield [%]
1	josiphos,[a] $[\{Rh(cod)Cl\}_2]$, AgOTf, Bu_4NI	65
2	josiphos,[a] $[Rh(cod)_2OTf]$	67
3	BBr_3	20
4	TMSOTf, Et_3N	95
5	TBDMSOTf, Et_3N	36
6	TfOH, Et_3N	–[b]

[a] Josiphos = (*S*)-1-[(R_p)-2-(di-*tert*-butylphosphanyl)ferrocenyl]ethyl-bis(2-methylphenyl)phosphane. [b] No reaction occurred; the starting material was recovered. cod = 1,5-cyclooctadiene, TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

Table 2: Lewis acid mediated oxabicyclo[2.2.1]heptene[9] ring opening.[a]

Entry	Substrate	Product	Yield [%]
1	 **9**	 **11**	95
2	 **12a**	 **12b**	92
3	 **13a**	 **13b**	67
4	 **14a**	 **14b**	73
5	 **15a**	 **15b**	50[b]

[a] Reaction conditions: substrate (0.07 mmol), TMSOTf (4.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2 (3 mL), 23 °C. [b] TBDMSOTf (4.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2 (3 mL), 23 °C; 50% based on recovered starting material, 80% conversion, 20% starting material recovered.

to product formation. This last result suggests that a Brønsted acid is not the active agent, and implicates the Lewis acidic silyl group as the catalyst.

We then proceeded to investigate the scope of the ring-opening reaction of additional oxabicyclo[2.2.1]heptenes. The reactions were conducted in CH_2Cl_2 at 23 °C in the presence of TMSOTf/Et_3N (Table 2). Like the free amine **9**, which formed the basis of our preliminary experiments, amide analogues were converted into the desired products in good to excellent yields (Table 2, entries 2 and 3). The transformation of **13a** demonstrated that the observed ring-opening reaction is not unique to systems constrained by an oxazolidinone ring. The amide **14a** also underwent ring opening (Table 2, entry 4). Interestingly, internal competition between two amides led to preferential formation of the quinoline nucleus **15b** (six-membered-ring formation) over the indole counterpart (five-membered-ring formation; Table 2, entry 5). Only under the reaction conditions with TMSOTf/Et_3N were **12b–15b** obtained; the starting materials were recovered when Rh catalysts were used.

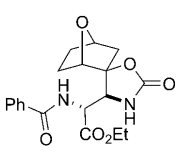
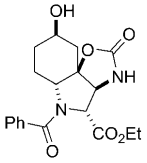
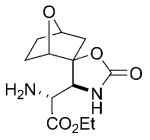
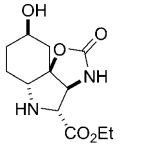
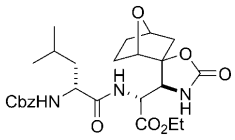
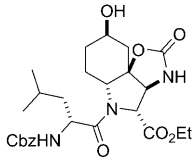
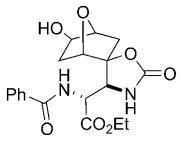
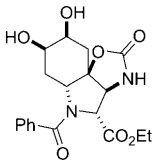
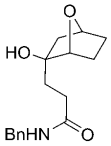
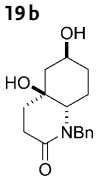
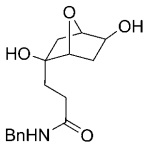
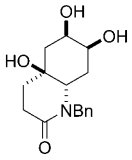
Although the cyclizations detailed in Table 2 are unprecedented, they can be rationalized readily as a consequence of the electrophilic activation of an allylic leaving group.[10] To examine the extent to which ring opening is facilitated by the embedded 5,6-olefin, we investigated the ring opening reaction of unactivated oxabicyclic substrates in which the C5–C6 bond is saturated. On the basis of the known reactivity profile of these systems and ethers in general, we did not anticipate the results observed with these substrates.

The analogous cyclization reaction proceeded quite readily in the absence of the olefin (Table 3) to afford [4.3.0] and [4.4.0] bicyclic products. The substrate scope is broad with respect to the nature of the nucleophilic group: both amides (Table 3, entries 1 and 3–4) and amines (entry 2) can be used, as well as inverse amides (entries 5 and 6). Furthermore, the cyclization proceeds well in the absence of entropic constraints (Table 3, entries 5 and 6), and the presence of an additional electron-withdrawing substituent does not impair the cyclization (Table 3, entry 4). The structure of the ring-opening products was confirmed by X-ray crystallographic analysis of the *p*-bromobenzoate ester of **20b**[11,12] (Table 3, entry 5). Having secured this structure, we were able to show that the reduction of **14b** (Table 2, entry 4; Pd/C, H_2) afforded **20b**. This structural correlation complemented extensive NMR spectroscopic studies to provide further confirmation of the product structures.[13] We speculate that the energetic driving force for this unprecedented transformation stems from the strain energy, estimated at 6.5 kcal mol^{-1}, of the oxabicycloheptanes.[14]

Several features of oxabicyclo[2.2.1]heptenes and -heptanes have previously been cleverly exploited in the elaboration of both with predictable levels of regio- and stereoselectivity. Examples include the inherent facial bias of an embedded olefin (*endo* versus *exo*) as well as the stereoelectronic influences of remote groups.[15] The same aspects may now be used in combination with the transformation we have described to provide access routes to ring structures common to a number of alkaloids, such as the Amaryllidaceae alkaloids[16] galwesine, galasine, and galanthine.

In conclusion, we have documented novel access to highly functionalized [4.3.0] and [4.4.0] bicyclic structures. This approach stems from the unexpected observation of a Lewis acid mediated ring-opening reaction of oxabicycloheptenes

Table 3: Lewis acid mediated oxabicyclo[2.2.1]heptane[9] ring opening.[a]

Entry	Substrate	Product	Yield [%]
1			89
	16a	**16b**	
2			89[b]
	17a	**17b**	
3			91
	18a	**18b**	
4			88
	19a	**19b**	
5			80
	20a	**20b**	
6			78
	21a	**21b**	

[a] Reaction conditions: substrate (0.07 mmol), TMSOTf (4.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2 (3 mL), 23 °C. [b] The product was isolated as the hydrochloride salt.

and heptanes. The ease with which these previously unexplored transformations take place is remarkable and opens new possibilities for strategic planning in complex-molecule synthesis.

Experimental Section

The oxabicycle (0.07 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) at 23 °C under argon. Triethylamine (51 μL, 0.4 mmol, 5 equiv) was added, followed by freshly distilled TMSOTf (53 μL, 0.3 mmol, 4 equiv, 95 %, Aldrich). The resulting solution was stirred at 23 °C, and the reaction was monitored by TLC. After completion (2–5 h), the reaction mixture was filtered through a plug of silica, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) and treated with a solution of HCl in MeOH (4 equiv, 1.0 M, Fluka). After 30 min, the solution was evaporated, and the crude mixture was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to afford the corresponding product.

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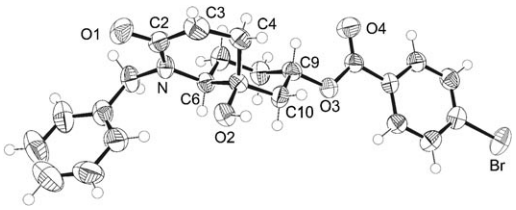
[9] The oxabicyclic substrates were prepared by an enantioselective Diels–Alder reaction of furan and bromoacrolein with the tryptophan-derived oxazaborolidine catalyst described by Corey and Loh (see references [3] and [4]). The L-tryptophan-derived catalyst was used for the reactions in entries 3 and 4 of Table 2 and entries 5 and 6 of Table 3; the D-tryptophan-derived catalyst was used for the reactions in entries 1 and 2 of Table 2 and entries 1–4 of Table 3.

[10] To the best of our knowledge, there is only one example in the literature of the opening of an oxabicycloheptene by displacement of a bridging C–O bond, namely, the ring opening of 2-methylthio-7-oxabicyclo[2.2.1]heptene by silyl enol ethers in the presence of TBDMSOTf: I. Yamamoto, K. Narasaka, *Chem. Lett.* **1995**, 1129. The ring opening proceeds by cleavage of the C–O bond, and net substitution occurs with retention of configuration. The stereochemical result underscores the fact that the reaction proceeds by heterolytic cleavage of the C–O bond to give a secondary carbocation, which is stabilized significantly by the vinyl sulfide.

[11] Crystallographic data for the *p*-bromobenzoate ester of **20b**: $C_{23}H_{24}BrNO_4$, $M_r = 458.35$, orthorhombic, space group $P2_12_12_1$, $a = 9.7647$ (2), $b = 10.6347$ (3), $c = 19.7861$ (5) Å, $V = 2054.68$ (9) Å^3, $\rho_{calcd} = 1.482$ Mgm^{-3}, $T = 223$ K, reflections collected: 18793, independent reflections: 4693 (R(int) = 0.15), R(all) = 0.0678, wR(gt) = 0.1315. CCDC 721256 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] ORTEP representation of the *p*-bromobenzoate ester of **20b** (probability ellipsoids at 50 %; Table 3, entry 5).



[13] We considered the mechanistic possibility of pinacol-type rearrangement sequences. However, the formation of the aminal product inevitably positions the tertiary hydroxy group at the other ring-fusion carbon atom. X-ray crystallographic analysis of the *p*-bromobenzoate ester of **20b** proved critical in ruling out this option.

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