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Ring Opening of Bicyclo[3.1.0]hexan-2-ones: A Versatile Synthetic Platform for the Construction of Substituted Benzoates

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Abstract: *Described is the development of a highly efficient 2π disrotatory ring-opening aromatization sequence using bicyclo[3.1.0]hexan-2-ones. This unprecedented transformation efficiently proceeds under thermal conditions and allows facile construction of uniquely substituted and polyfunctionalized benzoates. In the presence of either amines or alcohols formation of substituted anilines or ethers, respectively, is achieved. Additionally, the utility of this method was demonstrated in a short synthesis of sekikaic acid methyl ester.*

Substituted benzoic acid derivatives are ubiquitous in nature and they are highly valuable building blocks for organic synthesis.[1] Within this substance class, the 3-hydroxybenzoate structural motif constitutes a prominent subunit that can be found in several biologically active molecules (Figure 1).[2]

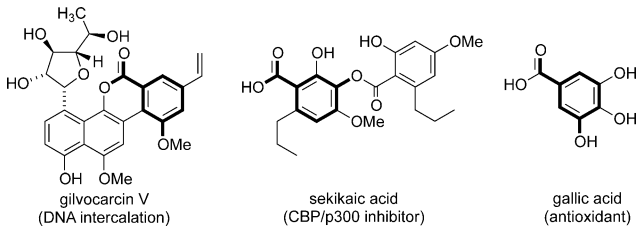


Figure 1. The 3-hydroxybenzoate structural motif as a component of biologically active natural products. LHMDS = lithium hexamethyldisilazane.

Conventional syntheses of polysubstituted 3-hydroxybenzoates from either aromatic (linear assembly) or acyclic (convergent assembly) precursors are complicated by difficulties arising from low reactivity and poor selectivity (Figure 2a, methods A–C). The electrophilic aromatic substitution of electron-poor benzoates (method A) requires harsh reaction conditions and shows limited functional-group tolerance.[3] For method B, the directing electronic effects of the ester and electron-donating substituents (Y = OR, NRR′) are mismatched and result in poor regioselectivity. Strategies based on the [4+2] cycloaddition of dienes with alkynoates (method C) usually require symmetrical substrates to allow formation of the desired 1,3-orientation.[4]

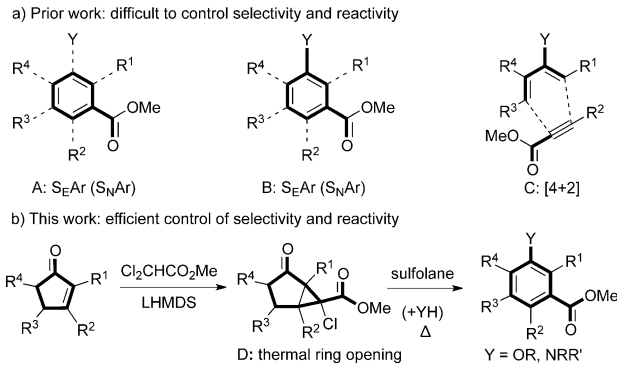
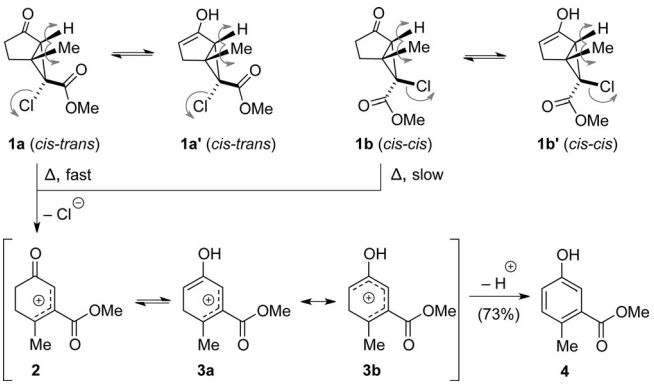


Figure 2. a) Traditional methods for the synthesis of polyfunctionalized benzoates. b) Thermal ring-opening aromatization of bicyclo-[3.1.0]hexan-2-ones.

As part of our recent efforts to develop new chemical methods for the synthesis of uniquely substituted phenols and naphthols,[5] we discovered that bicyclo[3.1.0]hexan-2-ones undergo an efficient thermal 2π disrotatory ring-opening aromatization sequence to afford a broad array of highly substituted benzoates (Figure 2b). By virtue of its substrate structure, this transformation enables simple control of selectivity and reactivity, and expands the repertoire of retrosynthetic bond disconnections for natural product synthesis. Herein, we report our preliminary results of this unprecedented transformation.[6–8]

We began our investigations with bicyclo[3.1.0]hexan-2-ones **1a/b** (d.r. = 4:1), which are readily available from the reaction of 3-methyl-2-cyclopenten-1-one with the lithium enolate of inexpensive methyl dichloroacetate (Scheme 1).[9]



Scheme 1. 2π Disrotatory ring-opening aromatization of a 4:1 diastereomeric mixture of **1a** and **1b** (sulfolane, 190 °C) to afford **4**.

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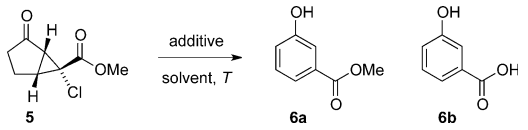
Conceptually, we envisioned the mixture of the *cis-trans* and *cis-cis* diastereomers **1a** and **1b**, respectively, to undergo a thermally allowed cyclopropyl allyl cation type ring opening (2π disrotatory) to afford **2**.[10] For the initial ring-opening step, the C–C bond cleavage with concomitant loss of chloride, we expected the reaction rate of **1a** and **1b** to be governed by the relative orientation of the substituents to the leaving group.[11] Monitoring the reaction by ^{1}H NMR spectroscopy proved that, after heating a solution of **1a** and **1b** in dimethyl [D_6]sulfoxide at 110 °C for 40 minutes, the diastereomeric ratio was changed from 4:1 to 1:3. While complete consumption of the major diastereomer **1a** was observed after 80 minutes, **1b** was reluctant to undergo ring opening at this temperature. However, exchanging dimethyl sulfoxide for sulfolane and increasing the temperature to 190 °C led to a drastic increase of the overall reaction rate and **4** was formed in 73 % yield.

Based on these preliminary results, we investigated the conversion of diastereomerically pure **5**[9] into **6** under varying reaction conditions (Table 1). An examination of various

Table 1: Thermal 2π disrotatory ring opening of **5** under varying reaction conditions.[a]



5 **6a** **6b**

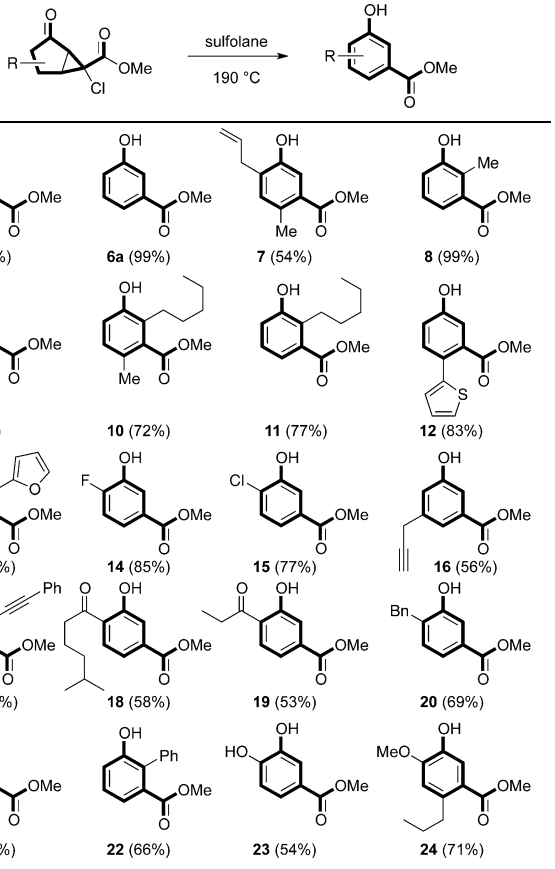
Entry	Solvent	Additive	T [°C]	t [h]	Yield [%]	
					6a	**6b**
1	sulfolane	none	190	0.25	99	0
2	sulfolane	none	140	8	41	0
3	NMP	none	190	1	99	0
4	ODCB	none	180	16	81	0
5	sulfolane	$AgNO_3$[b]	140	3	60	0
6	sulfolane	LiCl[c]	190	17	0	86
7	MeCN	*p*-TsOH[d]	80	16	0	0
8	TFE	none	70	3	0	0
9	sulfolane	DBU[e]	140	8	17	0
10	sulfolane	DIPEA[f]	140	8	56	0

[a] Yield of the isolated product. [b] 1.0 equiv $AgNO_3$. [c] 2.1 equiv LiCl. [d] 20 mol % *p*-TsOH. [e] 1.0 equiv DBU. [f] 1.0 equiv DIPEA. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, NMP = *N*-methyl-2-pyrrolidone, ODCB = 1,2-dichlorobenzene, TFE = 2,2,2-trifluoroethanol, Ts = 4-toluenesulfonyl.

solvents established that the reaction is efficiently promoted by polar, high-boiling solvents and proceeds fastest in sulfolane at 190 °C (entries 1–4). The effect of Lewis acids on the reaction yield at different temperatures was investigated next (entries 5–7). Thermolysis of **5** in the presence of $AgNO_3$ (140 °C) was less efficient and afforded **6a** in 60 % yield (entry 5). The use of excess lithium chloride at elevated temperatures (entry 6) enabled the direct formation of the acid **6b** (86 % yield). Low-boiling polar solvents (entries 7–8) were ineffective regardless of the additives and the starting material was recovered unchanged from these reactions. While enol formation was considered to play a crucial role for the stabilization of the initial carbocation intermediate and the final aromatization, attempts to promote the ring-opening reaction at 140 °C by addition of either DBU (entry 9) or DIPEA (entry 10) led to partial decomposition of **5** and diminished yields of **6a**.

The methodology outlined above was then applied to a wide range of bicyclo[3.1.0]hexan-2-ones which were synthesized from readily available 2-cyclopenten-1-ones. Table 2 depicts a number of examples of polysubstituted

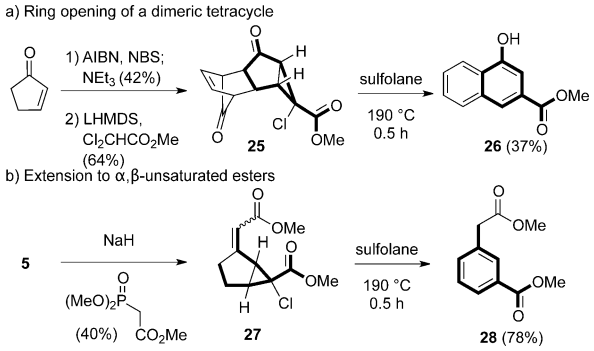
Table 2: Synthesis of substituted methyl 3-hydroxybenzoates from bicyclo[3.1.0]hexan-2-ones.[a]



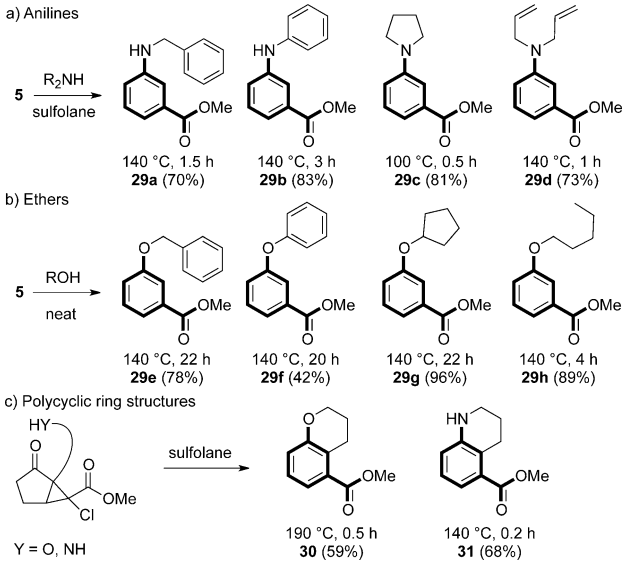
[a] Yield is that of the isolated product.

methyl 3-hydroxybenzoates. Reaction times were generally short (< 1 h) and an inert atmosphere was not required. When aliphatic groups were present, the products were formed in excellent yields of up to 99 %. Heteroaromatic substituents such as 2-thienyl or 2-furyl, and substrates containing fluoro or chloro substituents were also well tolerated under the reaction conditions.

With these results in hand, we tried to extend this methodology to other substrates. First, the tricycle **25**, obtained from the cyclopropanation of cyclopentadienone dimer,[12] was investigated (Scheme 2 a). This substrate underwent the ring opening with concomitant CO extrusion to give methyl 4-hydroxy-2-naphthoate (**26**). Application of the standard reaction conditions to the C2-elongated α,β-unsaturated ester **27** was also successful and provided the diester **28** in 78 % yield (Scheme 2 b).



Scheme 2. Extension of the ring-opening reaction. AIBN = 2, 2′-azoisobutyronitrile.

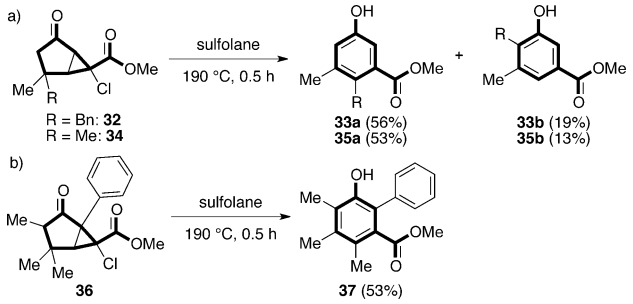


Scheme 3. Synthesis of a) aryl ethers, b) amines, and c) polycyclic ring structures in the presence of O or N nucleophiles.

To further explore the synthetic utility of our methodology, we investigated the in situ condensation of the carbonyl group with simple O and N nucleophiles (Scheme 3). Remarkably, in the presence of an amine (2 equiv) the ring-opening reaction of **5** to the aniline derivatives **29a–d** proceeded efficiently at temperatures as low as 100 °C. This observation supports our mechanistic hypothesis that enolization (enamine formation) plays a key role for the stabilization of the intermediate carbocation formed during the ring opening.

Substitution of sulfolane with high-boiling alcohols such as benzyl alcohol, phenol, cyclopentanol, or 1-pentanol allowed the straightforward synthesis of the protected phenols **29e–h** in good yield (Scheme 3b). Lower-boiling alcohols such as hexafluoro-2-propanol, 2,2,2-trifluoroethanol, or 2-methyl-1-butanol resulted in no product formation.[13] To demonstrate that this reaction also enables access to polycyclic ring structures, the nucleophile was tethered to the bicyclo[3.1.0]hexan-2-one framework as shown in Scheme 3c.

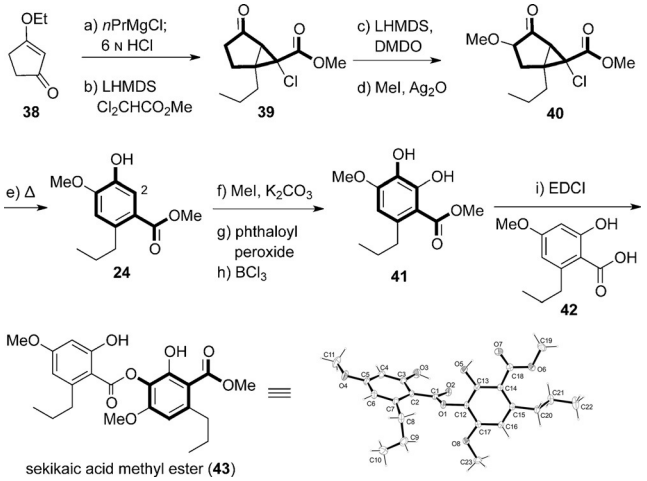
According to the previously presented mechanistic hypothesis, we envisioned substrates containing a quaternary



Scheme 4. Thermal ring opening with simultaneous [1,2] shift to give highly substituted methyl 3-hydroxybenzoates.

carbon center to undergo a consecutive ring opening/[1,2] shift (Scheme 4). To determine if this [1,2] shift can be triggered under the standard reaction conditions, we prepared the model substrates **32**, **34**, and **36**. To our delight, thermolysis of **32** and **34** led to the formation of the regioisomeric products **33a/b** and **35a/b**, respectively, in good yield, and they were readily separated by column chromatography on silica gel. For **32**, exclusive migration of the benzyl group in preference to the methyl group was observed. Installation of an additional substituent as shown for **36** enabled access to the hexasubstituted benzoate **37** in 53% yield.

Finally, we set out to apply this methodology to the synthesis of the highly potent GACKIX inhibitor sekikaic acid methyl ester (**43**; Scheme 5).[2d] We began our synthesis with 3-ethoxy-2-cyclopentenone (**38**) which was converted into **39** in two steps. Upon exposure of the lithium enolate of **39** to dimethyldioxirane and treatment of the resulting



Scheme 5. Synthesis and X-ray structure[16] of sekikaic acid methyl ester (**43**). Reagents and conditions: a) *n*PrMgCl, THF, then 6 N HCl, 74%; b) LHMDS, Cl_2CHCO_2Me, THF, −78 °C to 23 °C, 23%; c) LHMDS, DMDO, THF, −78 °C, 60%; d) MeI, Ag_2O, $MgSO_4$, 94%; e) sulfolane, 190 °C, 20 min, 71%; f) MeI, K_2CO_3, DMF, 55 °C, 94%; g) phthaloyl peroxide, TFE, then MeOH, aq. $NaHCO_3$, 94%; h) BCl_3, CH_2Cl_2, 0 °C, 59%; i) EDCI, DMAP, THF, **42**, 80%. DMAP = 4-(dimethylamino)pyridine, DMDO = dimethyldioxirane, DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, THF = tetrahydrofuran.

α-hydroxy ketone with methyl iodide, clean formation of the α-methoxy product was observed. Ring opening of **40** proceeded smoothly and afforded **24** in 71% yield. After methylation of the free phenol, the phthaloylperoxide-mediated oxidation recently developed by Siegel and co-workers[14] proceeded in high yield with excellent regioselectivity. Selective demethylation gave **41**, which was then coupled with acid **42**[15] to afford **43** in 80% yield. The structure of **43** was confirmed by single-crystal X-ray diffraction and the spectroscopic data were in full agreement with those reported previously.[2d]

In summary, we have developed a highly versatile methodology which converts bicyclo[3.1.0]hexan-2-ones into a broad array of valuable benzoates. In the presence of amines or alcohols, the ring-opening reaction proceeds by the intermediacy of an enamine or enol ether and provides straightforward access to aniline or ether derivatives. A broad application of this method for the synthesis of biologically active molecules is currently underway in our laboratories.

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Keywords: arenes · aromaticity · fused-ring systems · synthetic methods · X-ray diffraction

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[16] CCDC 1410728 (**43**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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