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Diels–Alder cycloadditions of 3,5-dibromo-2-pyrone with cycloalkenyl silyl ethers for the synthesis of bicarbocycles

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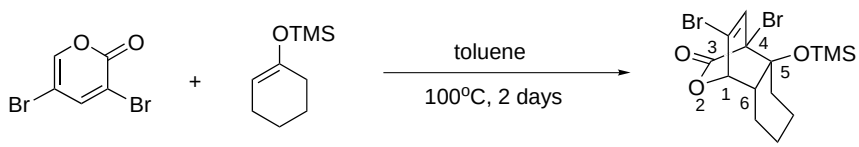
Abstract—3,5-Dibromo-2-pyrone underwent facile Diels–Alder [4+2] cycloadditions with cycloalkenyl silyl ethers to provide a series of tricyclolactones, with good to excellent chemical yields and stereoselectivity. The resulting cycloadducts could be readily converted into the corresponding bicarbocycles upon selective debromination and reductive lactone ring opening reactions.

Bicarbocycles are important structural cores that are present in number of terpene-based naturally occurring compounds including aristophyllides, eurycolactones, dolastane, spheroane as well as a series of illudane and taxane derivatives.[1] Many of them possess intriguing physiological activities, thus have drawn great attention for the syntheses over the past few decades. Among the various synthetic methods reported so far, Diels–Alder cycloaddition approach is arguably most popular and effective way for the construction of such structures.[2] A variety of dienes have been developed and used for these purposes, upon cycloadditions with appropriate dienophile partners. 2-Pyrone systems have also been employed as dienes for the same reason. Despite the many examples,[3] 2-pyrones themselves are not reactive dienes, because of their partial aromaticity.[4] Even after activation through the introduction of various polar substituents on the pyrone rings, their cycloadditions with sterically hindered dienophiles, therefore, often require harsh reaction conditions, leading to the aromatisation caused by CO_2 protrusion.[4]

We have recently reported that 3,5-dibromo-2-pyrone[5] is a potent ambident diene, being more reactive and stereoselective than mono-bromo-2-pyrones in both normal and inverse electron demand sense, thus capable of undergoing [4+2] Diels–Alder cycloadditions with the dienophiles that are sterically too hindered for the cycloadditions to occur with mono-bromo-2-pyrones.[6] A continued study revealed that 3,5-dibromo-2-pyrone cycloadded with sterically even more hindered, cyclohexenyl silyl ether to give rise to the tricyclolactone (Scheme 1). It is the first example in which 2-pyrone system has ever undergone cycloadditions with such sterically hindered, cycloalkenyl ethers. Envisioned that this sequential process would give us an easy access to a variety of bicarbocyclic cores, we undertook a systematic study on its cycloadditions with a series of cycloalkenyl silyl ethers. Table 1 summarises our results on the cycloadditions of 3,5-dibromo-2-pyrone, providing tricyclolactones.[7]

In Table 1, only *endo* isomers are shown for clarity. Cycloadditions with cyclic enol ethers up to seven-membered ones were highly stereospecific, providing mostly *endo*-products. On the other hand, the larger, eight-membered cyclic enol ether showed moderate *exo*-selectivity.



Scheme 1.

Keywords: Diels–Alder cycloaddition; 2-pyrones; carbocycles; dienes; lactone.
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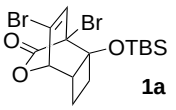
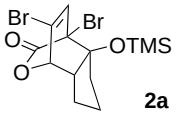
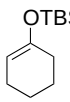
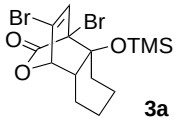
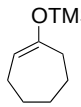
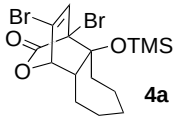
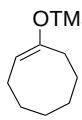
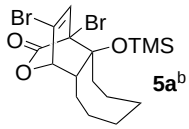
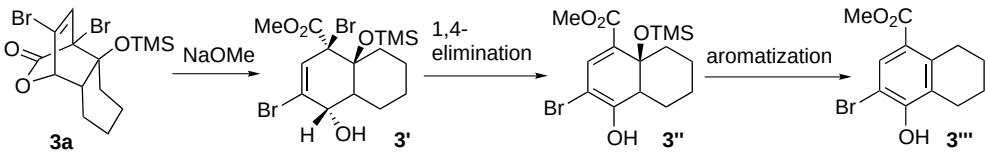
Table 1. Diels–Alder cycloadditions of 3,5-dibromo-2-pyrone with cycloalkenyl silyl ethers

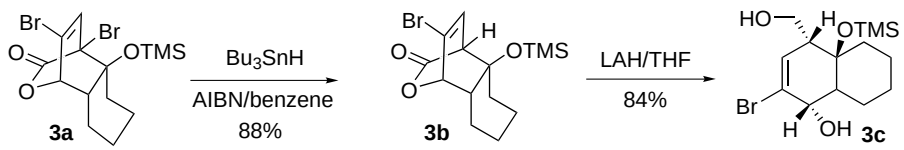
Dienophile	Cycloadduct	Time (days)	*endo*:*exo*	Yield (%)[a]
	 **1a**	1	93:7	85
	 **2a**	1	99:1	86
	 **3a**	2	99:1	73
	 **4a**	1	99:1	89
	 **5a**[b]	3	35:65	85

[a]Total (*endo* + *exo*) isolated yield.
[b]*exo*-Isomer was characterized in this case.

Non-commercial silyl enol ethers were prepared from the corresponding cyclic ketones upon deprotonation with LDA, followed by treatment with TMSCl or TBSCl. Relative stereochemistry of the *endo* and *exo* isomers was determined based on the magnitude of coupling constants between the protons at C6 and bridgehead (C1) positions. All the *endo* tricyclolactones **1a** through **5a** have the coupling constants between 2.0 and 2.8 Hz, while the *exo* ones have the coupling constants of 4.0 Hz range. Coupling of the bridgehead proton with 6-*endo* proton is found to be larger than that with 6-*exo* proton in all the analogous bicyclolactone systems reported so far.[6] Direct opening of the lactone bridge with NaOMe was accompanied with a concomitant 1,4-elimination and subsequent aromatisation as described below (Scheme 2). Removal of the tertiary alkyl bromide prior to the lactone ring opening was thus prerequisite. Although it initially looked a bit problematic, the bromine group at the tertiary carbon was successfully removed with high selectivity over the vinyl bromine under typical Bu_3SnH/AIBN condition. Lactone ring opening with either MeO^- or HO^- on the mono-bromo-adduct **3b**, however, still gave rise to the complex product mixture including substantial amount of aromatised products. Other unsuccessful attempts include aminolysis of the lactone ring using benzyl amine hydrochloride/sodium 2-ethyl hexanoate system.[8] The lactone bridge was eventually cleaved with $LiAlH_4$ to furnish the corresponding bicarbocyclic skeleton **3c** (Scheme 3).



Scheme 2.



Scheme 3.

In summary, we have found that 3,5-dibromo-2-pyrone underwent cycloadditions with highly sterically hindered cycloalkenyl enol ethers, for the first time, to afford tricyclolactones with good to excellent chemical yields and stereoselectivity. The resulting tricyclolactones were readily transformed into the corresponding bicarbocyclic skeletons upon selective debromination and subsequent reductive lactone ring opening reactions. Applications of our method toward the total synthesis of diterpenoid natural products are in progress.

Acknowledgements

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7. **Representative analytical data**: **3a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, $J=2.8$ Hz, 1H), 4.80–4.79 (m, 1H), 2.11–2.03 (m, 2H), 1.80–1.77 (m, 1H), 1.73–1.62 (m, 3H), 1.54–1.38 (m, 2H), 1.23–1.14 (m, 1H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 134.1, 118.1, 83.2, 77.7, 72.8, 49.3, 29.8, 23.8, 17.9, 15.5, 2.3; FT-IR; HRMS (CI) m/z $(M+1)^+$ calcd for $C_{14}H_{21}Br_2O_3Si$ 422.9626, found 422.9604. **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, $J_1=6.4$, $J_2=2.0$ Hz, 1H), 4.76 (dd, $J_1=2.0$, $J_2=1.6$ Hz, 1H), 3.54 (d, $J=6.4$ Hz, 1H), 1.86 (dd, $J_1=13.2$, $J_2=6.0$ Hz, 1H), 1.79–1.35 (m, 8H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 127.6, 120.1, 84.3, 74.0, 56.5, 48.4, 31.8, 22.9, 18.1, 15.5, 2.1; FT-IR; HRMS (EI) m/z $(M+1)^+$ calcd for $C_{14}H_{21}BrO_3Si$ 344.0443, found 344.0465. **3c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, $J=2.4$ Hz, 1H), 4.36–4.34 (m, 1H), 3.92 (dd, $J_1=10.0$, $J_2=5.6$ Hz, 1H), 3.62–3.36 (m, 1H), 2.56–2.51 (m, 1H), 2.12–1.94 (m, 1H), 1.77–1.60 (m, 3H), 1.50–1.26 (m, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.6, 125.2, 74.8, 74.4, 61.7, 52.3, 44.6, 29.8, 23.6, 21.7, 20.4, 2.6; FT-IR; HRMS (EI) m/z $(M+1)^+$ calcd for $C_{14}H_{25}BrO_3Si$ 348.0756, found 348.0741.
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