ORGANIC LETTERS

2013
Vol. 15, No. 12
3130–3133

Total Syntheses of Cannabicyclol, Clusiacyclol A and B, Iso-Eriobrucinol A and B, and Eriobrucinol

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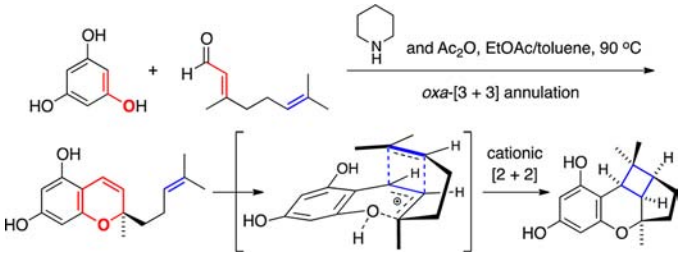
Received May 13, 2013

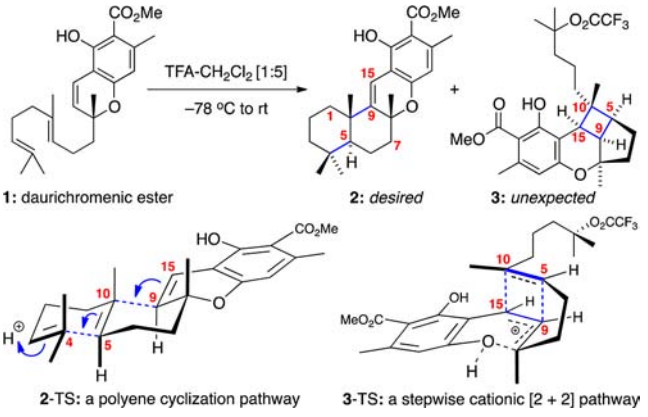
ABSTRACT



Total syntheses of a series of chromane natural products that contain a cyclobutane ring are described. A unified theme in the strategy employed for all these syntheses is an *oxa*-[3 + 3] annulation for constructing the chromane nucleus and a stepwise cationic [2 + 2] cycloaddition for the cyclobutane formation. More importantly, the two reactions could be rendered in tandem, thereby providing an expeditious approach to this family of natural products.

We had reported[1] a Stork–Eschenmoser–Johnson polyene cyclization cascade[2] employing daurichromenic ester **1** that constituted a bioinspired strategy[4,5] for a facile total synthesis of hongoquercin A through the desired tetracyclic intermediate **2** [Scheme 1].[1,3] In this study, we uncovered a significant and unexpected side-product **3**, which was likely derived through a rare cationic [2 + 2] cycloaddition [see **3**-TS] that is both biosynthetic in origin[6] and mechanistically analogous to Gassman's work with vinyl acetals.[7,8] While this unexpected finding allowed us to fully expand and develop Gassman's reaction into a useful

Scheme 1. An Unexpected Cationic [2 + 2] Pathway



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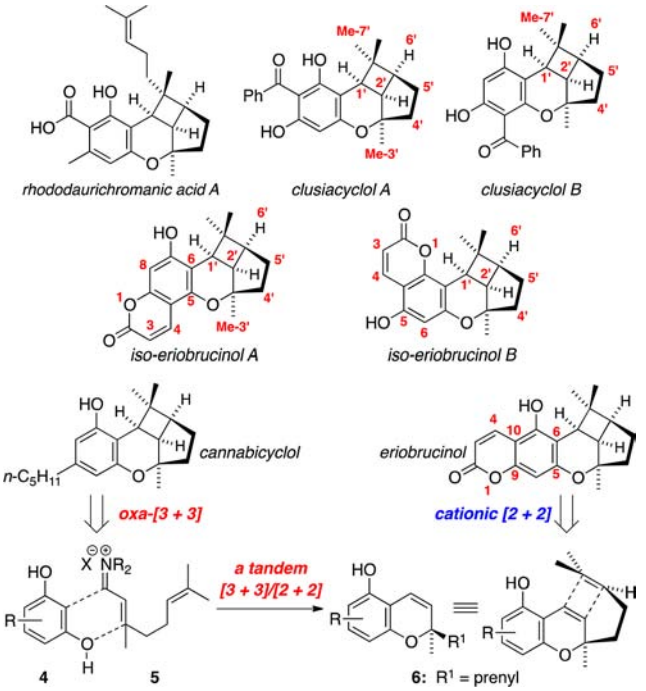
10.1021/ol401335u
Published on Web 06/03/2013

thermally driven stepwise [2 + 2] cycloaddition,[9,10] we have been drawn back to this original cationic cycloaddition because of (a) its potential in constructing cyclobutane containing natural products specifically those fused with a chromane nucleus[11−14] such as rhododaurichromanic acid A [see Scheme 2][15] and (b) there were disagreements in the early literature regarding the prospect of an acid-promoted cyclobutane formation. More significantly, we recognized that we could not only apply our *oxa*-[3 + 3] annulation[16−18] along with this stepwise cationic [2 + 2] cycloaddition to access these targets but also develop a formidable cascade in natural product synthesis if they are deployed in tandem.[19] We wish to report our success in developing such a strategy through total syntheses of these natural products.

The general concept to cyclobutane containing chromane natural products such as clusiacyclol A and B,[13a,20] iso-eriobrucinol A and B, eriobricinol,[21,22] and cannabicyclol[23] is shown in Scheme 2. While synthesis of the chromanyl nucleus would be achieved via an *oxa*-[3 + 3] annulation of phenols **4** with α,β-unsaturated iminium salts **5**, construction of the cyclobutane ring would feature an acid promoted cationic intramolecular [2 + 2] cycloaddition of **6**. This strategy could be carried in a sequential manner or rendered in a tandem manner.

Scheme 2. A General Synthetic Approach



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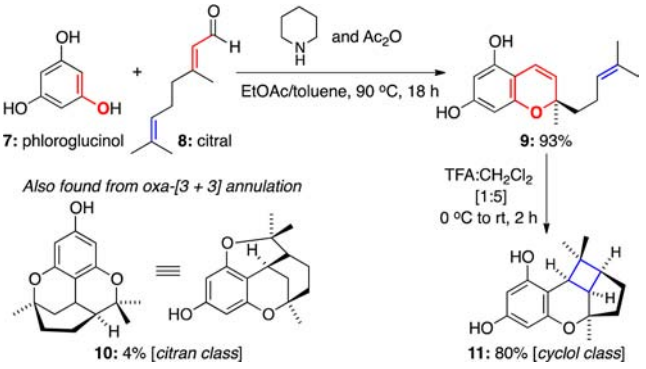
The sequential aspect of this strategy was quickly established using phloroglucinol **7**. The *oxa*-[3 + 3] annulation of **7** proceeded smoothly with the iminium salt generated from citral **8** using our piperidine and acetic anhydride conditions,[24,25] leading to chromene **9**[26] in 93% yield [Scheme 3]. Intriguingly, we also managed to isolate and identify a very small amount of tetracycle **10**, which has been referred to as the "citran" class of these natural products.[12−14,18f,18i,18m,20−23] The ensuing TFA-promoted cationic [2 + 2] cycloaddition of **9** gave chromanyl cyclobutane **11** in 80% yield. Chromanyl cyclobutanes such as **11** has been named as the "cyclol" class. The structural integrity of **10** and **11** could be unambiguously confirmed using single crystal X-ray structures with the latter through its diester derivative **14** [Figure 1].[27] The same sequence of annulation followed by cycloaddition is general and could be carried out also using olivetol **12**,[28] leading to a facile synthesis of cannabicyclol[23] [Scheme 4].

Scheme 3. Establishing the Sequential Sequence



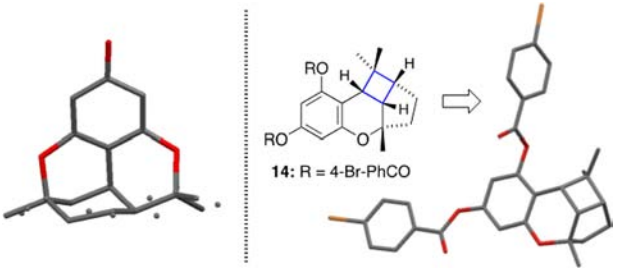


Figure 1. X-ray structures of tetracycle **10** and diester **14**.

(24) (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Wei, L.-L.; Sklenicka, H. M.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729.

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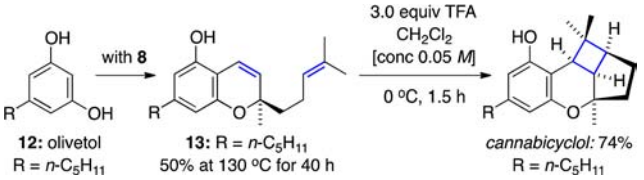
(26) See Supporting Information.

Scheme 4. Synthesis of Cannabicyclol



Mechanistically, we believed that citran products such as **10** are derived from chromene **9** through an iterative cationic sequence through intermediates such as **15** and **16** [Scheme 5]. It is noteworthy that even upon standing in $CDCl_3$ at rt, chromene **9** could be readily converted to **10**. However, under the reaction conditions adopted for the [2 + 2] cycloaddition, neither the conversion of tetracycle **10** to **11** nor the reverse was feasible. This observation suggests that the proposed stepwise cationic pathway from **9** to **10** may not be reversible. Alternatively, a hetero-Diels−Alder cycloaddition via the *ortho*-quinone methide **10**-TS, which can be envisioned either from **15** and/or from **9** via a tautomeric process, provides another possible mechanistic pathway.[29] Although a retro-Diels−Alder is possible, the need to break the aromaticity would present an impediment to this reversibility.

We next examined if the *oxa*-[3 + 3] annulation proceed in tandem with the cationic [2 + 2] cycloaddition. While the annulation conditions still employed piperidine and acetic anhydride, the cycloaddition had to rely on the presence of much weaker HOAc [Table 1]. Consequently, to make this process feasible, the reaction temperature had to be raised to 90 °C, along with an extended reaction time [entry 1 vs entries 2 and 3]. A number of aromatic solvents were screened as the cosolvent with EtOAc. With the exceptions of benzene [entry 5] and 4-NO_2-benzene [entry 9], all other aromatic co-solvents led to an appreciable amount of the desired product **11**. It is noteworthy that, unlike the case with TFA, tetracycle **10** was the major product under these conditions.

Scheme 5. Cationic versus Hetero-Diels−Alder Pathway to **10**

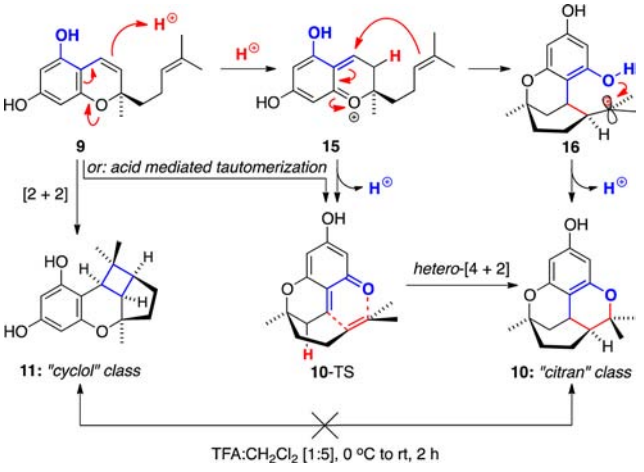
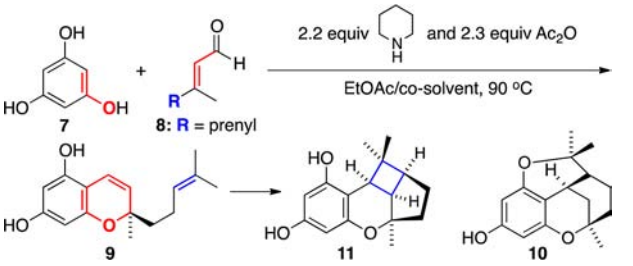


Table 1. A Tandem *Oxa*-[3 + 3] Annulation–Cationic [2 + 2][a,b]

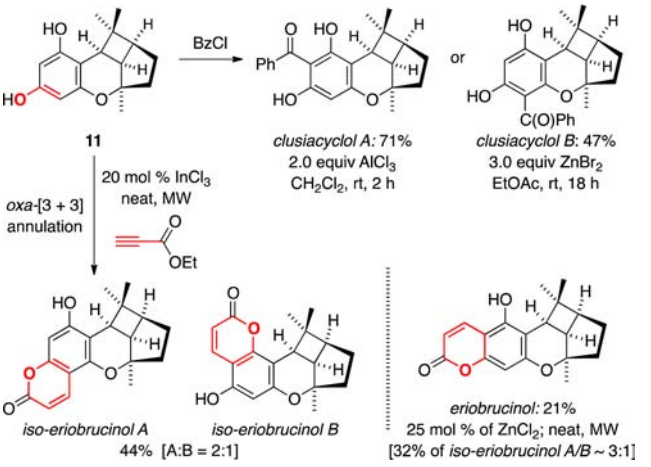


			yields [%] of:		
entry	cosolvent	time [h]	**9**	**11**	**10**
1	toluene	18	60	15	17
2	toluene	40	20	29	42
3	toluene	60	0	26 (25)	43 (40)
4	toluene[c]	60	0	18	36
5	benzene	60	13 (11)	19 (18)	42 (39)
6	xylene	60	0	25 (24)	38 (35)
7	3-Br-toluene	60	0	27	35
8	4-Br-toluene	60	0	23 (23)	32 (28)
9	4-NO_2-C_6H_5	60	0	0	0

[a] NMR yields using CH_2Br_2 as the internal standard. Yields in the parentheses are isolated. [b] The crude reaction mixture was initially quenched by sat aq $NaHCO_3$ before workup. [c] 1.2 equiv of piperidine and 1.3 equiv of Ac_2O were used.

The completion of total syntheses is shown in Scheme 6. Chromanyl cyclobutane **11** could be readily converted to clusiacyclol A ad B via *C*-benzoylation[18m] using $AlCl_3$ and $ZnBr_2$, respectively. In the latter case, a mono-*O*-benzyolation product was also found in 43% yield. The nature of Lewis acids appears to be critical in the regioselectivity of the benzoylation, and we are certain of the rationale behind this phenomenon at this point.[26]

Scheme 6. Completion of Total Syntheses



On the other hand, a Lewis acid promoted *oxa*-[3 + 3] annulation of **11** with ethyl propiolate[30] could afford a mixture of iso-eriobrucinol A and B in 44% in a 2:1 ratio. It is again intriguing that the nature of Lewis acids exerts an influence on the regioselectivity of these annulations.[26] With $InCl_3$, no eriobrucinol was observed, but the use of $ZnCl_2$ gave eriobrucinol in 21% yield, albeit iso-eriobrucinol A and B remain as the major products.[31] It is noteworthy that while these yields are modest, the overall sequence is very short in leading to complex tetra- or pentacyclic manifolds.

We have described the total syntheses of a series of chromane natural products that contain a cyclobutane ring. A unified theme in the strategy in all these syntheses is an *oxa*-[3 + 3] annulation for construction of the chromane nucleus and a stepwise cationic [2 + 2] cycloaddition for the cyclobutane formation. The annulation and cycloaddition could be rendered in tandem, leading to an expeditious approach to this family of natural products.

Acknowledgment. H.S.K. and H.L. contributed equally in this work. We thank the NSF [CHE1012198] for general support. Y.T. thanks the Natural Science Foundation of China for generous funding [Nos. 21172169 and 21172168]. We also thank Dr. Victor Young of The University of Minnesota and Dr. Haibin Song of Nankai University for providing X-ray structure and data analysis.

Supporting Information Available. Experimental procedures, X-ray data, NMR spectra, and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(27) Compound **11** has been documented, but the reported ^1H and ^{13}C NMR characterization data were incomplete and there was no stereochemistry assigned therein. See: Eisohly, H. N.; Turner, C. E.; Clark, A. M.; Eisohly, M. A. *J. Pharm. Sci.* **1982**, *71*, 1319. Upon repeating their reaction, in our hands, we only found chromene **9** in 7% yield and chromanyl cyclobutane **11** was not observed.

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(30) (a) Zehnder, L. R.; Dahl, J. W.; Hsung, R. P. *Tetrahedron Lett.* **2000**, *41*, 1901. Also see: (b) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A.-L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78.

(31) One referee made an excellent observation for which we appreciate and actually also have considered. In principle, iso-eriobrucinol B and eriobrucinol can equilibrate under these conditions. Eriobrucinol could be more stable than iso-eriobrucinol B due to the steric interaction between the pyrone unit and C7′ gem-dimethyl motif. To the best of our ability, when subjecting to the $InCl_3$ and $ZnCl_2$ reaction conditions, there was no observable equilibration from a mixture of iso-eriobrucinol A and B to eriobrucinol.