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Acid-Catalyzed Synthesis of Bicyclo[3.*n*.1]alkenediones

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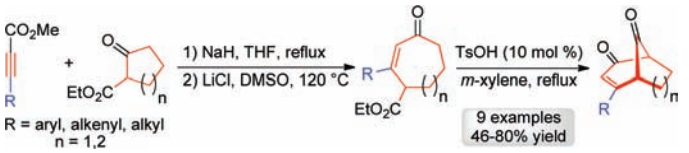
ABSTRACT



An acid-catalyzed Dieckmann-type reaction has been developed to access functionalized bicyclo[3.2.1]alkenediones. This methodology has been successfully extended to more substituted and larger ring homologues, providing a new and efficient route to the core of numerous attractive natural products and their analogues.

Densely substituted bicyclo[*m*.*n*.1]alkanones are common to numerous biologically interesting and synthetically challenging natural products (Figure 1). Widely represented by the polyphenols and phloroglucinol derivatives,[1] like the radical scavenger vitisinol D (**1**),[2] or the potential anti-Alzheimer agent garsubellin A (**2**),[3] this framework is also present in welwistatin (**3**),[4] famous for its promising anticancer activity.

Current methodologies to access the [3.*n*.1] carbon skeleton rely predominantly on [5 + 2] cycloadditions[5] or on sequential α,α′-double addition of a cyclic ketone to an acrylate derivative or an Effenberger cyclization.[6]

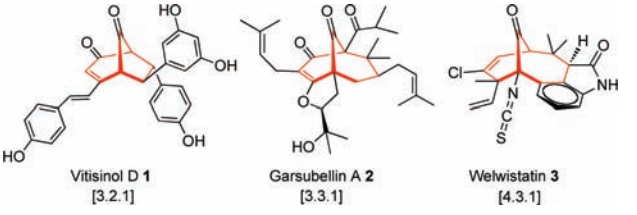


Figure 1. Naturally occurring bicyclo[*m*.*n*.1]alkanone structures.

More recent studies for the synthesis of these bicyclo frameworks include, for example, gold-catalyzed cyclization

(1) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.
(2) Huang, Y.-L.; Tsai, W.-J.; Shen, C.-C.; Chen, C.-C. *J. Nat. Prod.* **2005**, *68*, 217.
(3) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947.
(4) (a) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935. (b) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241. (c) Zhang, X.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288.
(5) (a) Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Romo, J. *Tetrahedron Lett.* **1965**, *6*, 1577. (b) Büchi, G.; Mak, C.-P. *J. Am. Chem. Soc.* **1977**, *99*, 8073. (c) Büchi, G.; Chu, P.-S. *Tetrahedron* **1981**, *37*, 4509. (d) Büchi, G.; Chu, P.-S. *J. Org. Chem.* **1978**, *43*, 3717. (e) Engler, T. A.; Wei, D.; Letavic, M. A. *Tetrahedron Lett.* **1993**, *34*, 1429. (f) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588. (g) Engler, T. A.; Meduna, S. P.; LaTessa, K. O.; Chai, W. *J. Org. Chem.* **1996**, *61*, 8598. (h) Engler, T. A.; Letavic, M. A.; Iyengar, R.; LaTessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391.
(6) (a) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895. (b) Schick, H.; Roatsch, B.; Schwarz, H.; Hauser, A.; Schwarz, S. *Liebigs Ann. Chem.* **1992**, 419. (c) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642. Effenberger cyclization: (d) Schönwälder, K.-H.; Kollat, P.; Stezowski, J. J.; Effenberger, F. *Chem. Ber.* **1984**, *117*, 3280. (e) Rodeschini, V.; Simpkins, N. S.; Wilson., C. *J. Org. Chem.* **2007**, *72*, 4265. (f) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287.
(7) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236.

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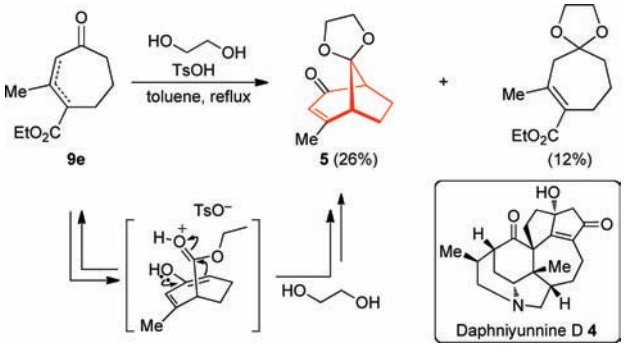
of silyl enol ethers onto pendant alkyne functionality[7] or combined rhenium−TBAF catalysis in ketone to ester addition reactions.[8]

During recent work within our group focusing on the synthesis of daphniyunnine D (**4**),[9] we unexpectedly observed the formation of this intriguing structural motif. While attempting to protect the carbonyl of the isomeric enone **9e** with ethylene glycol under TsOH catalysis, we observed the formation of the expected ketal only in 12% yield accompanied by 26% of the monoprotected bicyclo[3.2.1]alkenedione **5**. This compound was believed to result from an acid promoted Dieckmann-type reaction of the enol form of the cyclic enone onto the activated ester moiety,[10] followed by an in situ ketalization.[11]

To investigate and develop this appealing process we chose the readily accessible model substrate **9a** for an optimization study. Following a modification of a previously published reaction,[12] it was found that the keto diester **8a** could be obtained in good yield by reacting the commercially available compounds **6a** and **7** in the presence of sodium hydride. Subsequent Krapcho dealkyloxycarbonylation provided an isomeric mixture of the cyclization substrate **9a**.

Scheme 1. Unexpected Observation of the Formation of **5** and Proposed Mechanistic Pathway



With our model substrate in hand, the development of optimum cyclization conditions was addressed by examining various reaction parameters. We reasoned that if the mechanistic pathway was as shown in Scheme 1, cyclization should proceed in the absence of ethylene glycol. This was the case: by refluxing **9a** in toluene in the presence of 10 mol % of TsOH, the diketone **10a** was isolated in an encouraging 46% yield (Table 1, entry 1). Moreover, single-crystal X-ray diffraction of **10a** unambiguously confirmed its structure (Figure 2).[13]

Lowering the temperature was deleterious to the yield with only 15% of the product being isolated (entry 2). By changing the solvent to 1,4-dioxane with a boiling point similar to that of toluene, no product formation was observed. Therefore, reactions were performed in higher boiling point solvents and gave improved yields of 54% and 52% for *m*-xylene and 1,1,2,2-tetrachloroethane, respectively (entries 4 and 5). On the other hand, use of polar

Scheme 2. Preparation of the Model Substrate **9a**

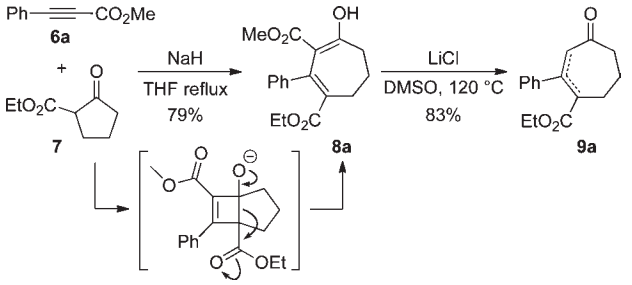
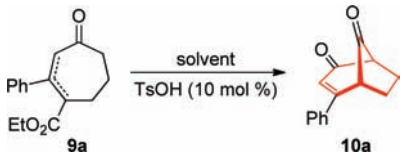


Table 1. Optimization of the TsOH-Catalyzed Cyclization



entry	solvent conditions	yield[a] (%)
1	toluene, reflux (0.2 M)	46
2	toluene, 90 °C (0.2 M)	15
3	1,4-dioxane, reflux (0.2 M)	0
4	*m*-xylene, reflux (0.2 M)	54
5	TCE,[b] reflux (0.2 M)	52
6	DMF or DMSO, 145 °C (0.2 M)	0
7	***m*-xylene, reflux (0.05 M)**	**80**
8	*m*-xylene, reflux (0.025 M)	73
9	*m*-xylene, reflux (0.05 M)[c]	71
10	mesitylene, reflux (0.05 M)	60
11	*m*-xylene, reflux (0.05 M)[d]	0

[a] Yields after flash chromatography. [b] TCE = 1,1,2,2-tetrachloroethane. [c] Using 5 mol % of TsOH. [d] Without TsOH.

(8) Kuninobu, Y.; Morita, J.; Nishi, M.; Kawata, A.; Takai, K. *Org. Lett.* **2009**, *11*, 2535.

(9) Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 553.

(10) Two independent cases of related acidic cyclization reactions have been reported: (a) Askam, V.; Quazi, T. U. *J. Chem. Soc., Chem. Commun.* **1975**, 798. (b) Sedgeworth, J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2677.

(11) Harding, K. E.; Clement, B. A.; Moreno, L.; Peter-Katalinic, J. *J. Org. Chem.* **1981**, *46*, 940.

(12) (a) Lennon, M.; McLean, A.; McWatt, I.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1828. (b) Frew, A. J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1245. (c) Frew, A. J.; Proctor, G. R.; Silverton, J. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1251.

(13) Data were collected at low temperature [Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr.* 1986, *19*, 105] using an Enraf-Nonius KCCD diffractometer [Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode Methods Enzymol*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: New York, 1997; p 276]. The crystal structure of **10a** was solved using SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* 1994, *27*, 435] and refined using the CRYSTALS software suite [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* 2003, *36*, 1487], as per the Supporting Information (CIF).

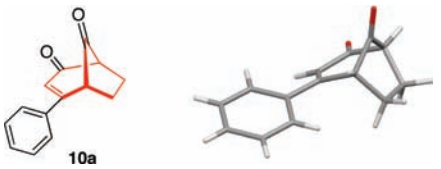


Figure 2. Single-crystal X-ray structure of **10a**.

solvents like DMF or DMSO at 145 °C only resulted in decomposition (entry 6).

Lowering the concentration was found to be beneficial with the optimal reaction being performed at 0.05 M to obtain a yield of 80% (entry 7). Decreasing the amount of TsOH or increasing the temperature by using boiling mesitylene proved to be less favorable, and a control experiment without acid showed no product formation whatsoever.[14] After determination of the optimal reaction conditions the scope of the reaction was explored by preparing seven-membered ring substrates with various β-substituents (R) (with respect to the ketone).

The two-step procedure developed for the preparation of **9a** (Scheme 2) was successfully applied to the synthesis of various cyclic 1,5-ketoesters **9** (Scheme 3). Aryl, alkenyl, and alkyl substituents were introduced opening the route to functionalized bicyclo[3.2.1]alkenediones. In the case of the *N*-Boc-protected indole substituent of **8d**, the conditions of the employed Krapcho reaction also resulted in the removal of the Boc group.[15] Application of the optimized cyclization conditions to these new substrates allowed the preparation of a range of new bicyclic products (Scheme 4).

Phenyl- and 4-trifluoromethyl phenyl-substituted substrates both gave high yields of the product, while electron-rich aryl substituents led to the expected product but with slightly lower yields (67% and 63% for **10c** and **10d**, respectively). Methyl- and *n*-butyl-substituted keto esters **9e** and **9f** successfully led to the alkyl-substituted bicyclo-[3.2.1]alkenediones **10e** and **10f** in 59% and 57% yields, respectively. Disappointingly, when the same procedure was applied to the benzyloxyethyl-substituted substrate **9g** no reaction was observed, and a longer reaction time only resulted in slow degradation. More interestingly, product **10h** was formed with 78% yield giving a direct access to the core of vitisinol D (**1**). Pleasingly, when the 8-membered ring analogue of **9a** was submitted to the optimized cyclization conditions, the bicyclo[3.3.1]alkenone **10i** was obtained in 53% yield, proving the potential access to larger ring systems.[16] The α-allylated product **10j** isolated in 46% yield from **9j**[17] demonstrates the possibility of accessing more functionalized

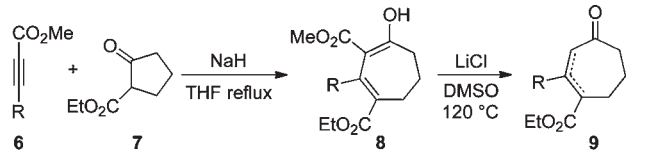
(14) Since TBAF was described as a basic promoting agent for this type of reaction (ref 8) TsOH was also replaced by TBAF, but only decomposition of the starting material was observed in this case.

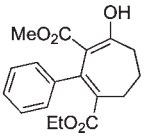
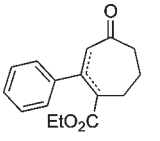
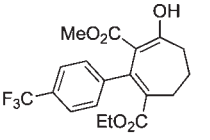
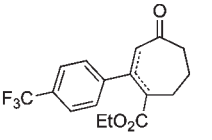
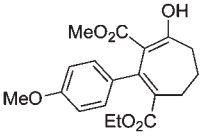
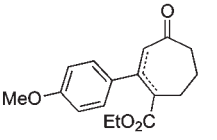
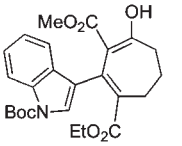
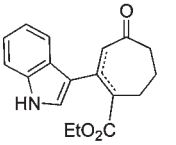
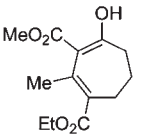
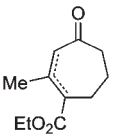
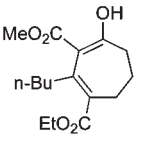
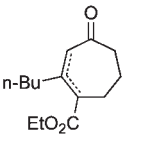
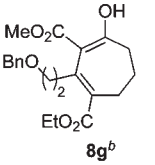
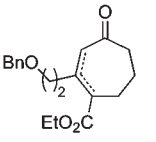
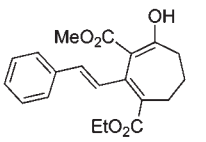
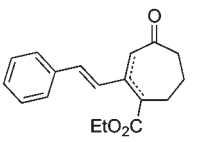
(15) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19.

(16) However, the 9-membered cyclization substrate proved to be unreactive under TsOH catalysis, and no product was observed.

(17) For the preparation of **9j** from **9e**, see the Supporting Information.

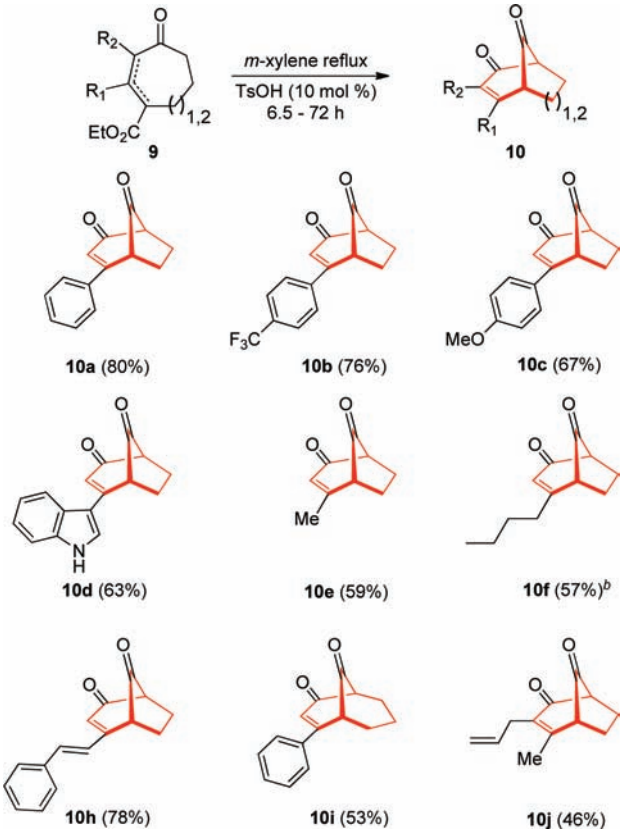
Scheme 3. Preparation of Cyclization Substrates[a]



entry	**8** (yield)	**9** (yield)
1	 **8a** (79%)	 **9a** (83%)
2	 **8b** (73%)	 **9b** (75%)
3	 **8c**[b]	 **9c** (78%)[c]
4	 **8d**[b]	 **9d**, (37%)[c]
5	 **8e** (81%)	 **9e** (88%)
6	 **8f** (69%)	 **9f** (92%)
7	 **8g**[b]	 **9g** (48%)[c]
8	 **8h** (83%)	 **9h** (70%)

[a] Yields after flash chromatography. [b] Used crude. [c] Yield over two steps.

Scheme 4. Synthesis of Bicyclo[3.*n*.1]alkenediones[a]

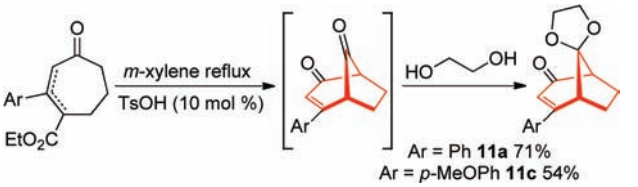


[a] Yields after flash chromatography. [b] Using 20 mol % of TsOH.

cores. This last result is of particular interest considering that a large number of natural products bear subsituents in the α-position, like the prenyl group of garsubellin A (**2**).

One benefit of this method, as indicated by our initial discovery (Scheme 1), is that the reactive carbonyl groups can be differentiated under the employed reaction conditions by the staged addition of ethylene glycol. Following the complete conversion of the starting material **9a** to its cyclization product, ethylene glycol was injected into the same pot, and the monoprotected bicyclic product **11a** was afforded in 71% yield (Scheme 5). When the same procedure was applied to the keto ester **9c**, the corresponding *p*-MeO derivative was afforded in 54% yield for the sequence.

Scheme 5. One-Pot Cyclization/Protection[a]



[a] Yields after purification by flash chromatography.

In summary we have described an efficient TsOH-catalyzed route to functionalized bicyclo[3.*n*.1]alkenediones. Products were typically isolated in good overall yield, and it has been shown that a one-pot procedure allows access to a monoprotected form of these products. This methodolody is currently being applied to the total synthesis of vitisinol D (**1**) and related compounds, and the results will be reported in due course.

Acknowledgment. We thank the EPSRC (a PDRA Fellowship to B.D. and a Leadership Fellowship to D.J.D.), Andrew Kyle of the Department of Chemistry, University of Oxford, for X-ray structure determination, and the Oxford Chemical Crystallography Service for the use of the instrumentation.

Supporting Information Available. Experimental details and characterization data for all new compounds and CIF file of **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.