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Four Nucleophilic Additions to Alkenynedioic Acid Derivatives in Tandem; Efficient One-Pot Synthesis of Bicyclo[4.2.0]octenols

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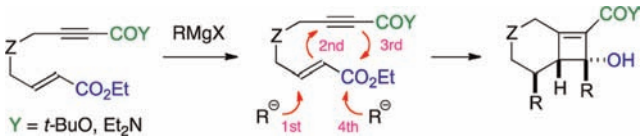
ABSTRACT



When alkenynedioic acid derivatives were treated with a Grignard reagent, tandem cyclization and the incorporation of two molecules of the Grignard reagent occurred to give stereodefined bicyclo[4.2.0]octenols via four nucleophilic additions.

Intermolecular nucleophilic addition to α,ω-unsaturated carbonyl compounds **1** (first addition in Scheme 1) followed by spontaneous cyclization (second addition) from **2** to **3** is a useful synthetic method to prepare cyclic compounds **4**, often in a regio- and stereoselective manner.[1,2] This transformation has found numerous applications by employing various combinations of nucleophiles and unsaturated carbonyl compounds.[3] Although it is likely that intermediate enolate **3** is capable of nucleophilic addition to the neighboring carbonyl group (third addition) to give cyclobutanones (or cyclobutenones) **5**, to the best of our knowledge, such a route has not been documented. Here we report this alternative path that features the third addition and even a subsequent fourth addition with the excess nucleophile, ultimately providing bicyclic compound **6** in one pot. Scheme 2 summarizes the overall reaction consisting of four consecutive nucleophilic additions, which should satisfy current criteria for highly efficient synthetic transformations.

During our studies on the cyclization of α,ω-unsaturated carbonyl compounds **1**,[4] we examined their reactions with various organometallic reagents in the presence or absence of transition metal catalysts. When enyne **7** was

(1) For reviews on the preparation of cyclic compounds by double nucleophilic additions, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; pp 48–156. (b) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010–1022. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366. (d) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.

(2) For general reviews on tandem reactions, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.—Eur. J.* **2009**, *15*, 12168–12179. (c) Alba, A.-N.; Companyó, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432–1474. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (e) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341–5378. (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (g) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413–422. (h) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564. (i) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (j) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159. (k) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. (l) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (m) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163.

(3) For recent examples, see: (a) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2011**, *13*, 808–811. (b) Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M. *Org. Lett.* **2010**, *12*, 5772–5775. (c) Tan, J.; Xu, X.; Zhang, L.; Li, Y.; Liu, Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 2868–2872. (d) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959–1962. (e) Oswald, C. L.; Peterson, J. A.; Lam, H. W. *Org. Lett.* **2009**, *11*, 4504–4507. (f) Sánchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536–7539.

(4) (a) Hata, T.; Hirone, N.; Sujaku, S.; Nakano, K.; Urabe, H. *Org. Lett.* **2008**, *10*, 5031–5033. (b) Hata, T.; Sujaku, S.; Hirone, N.; Nakano, K.; Imoto, J.; Imade, H.; Urabe, H. *Chem.—Eur. J.* **2011**, *17*, 14593–14602.

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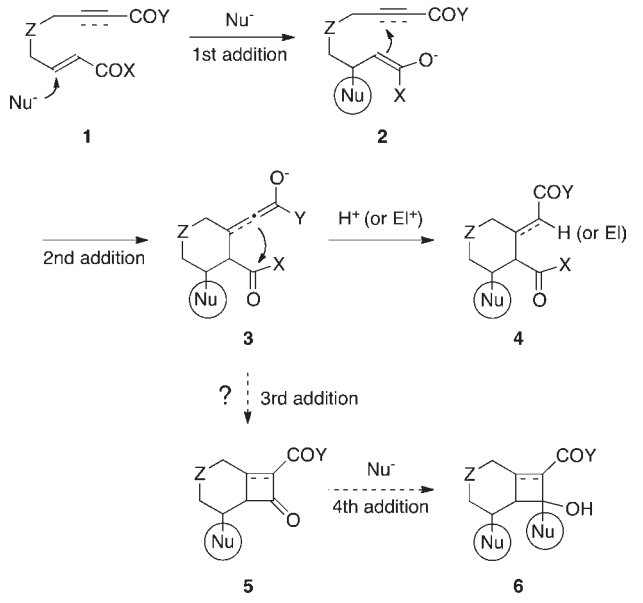
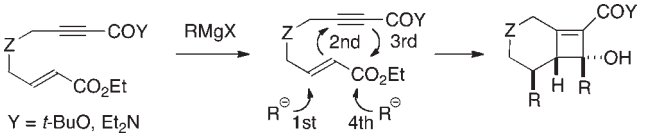
Scheme 1. Multiple Nucleophilic Additions Leading to Different Ring Systems

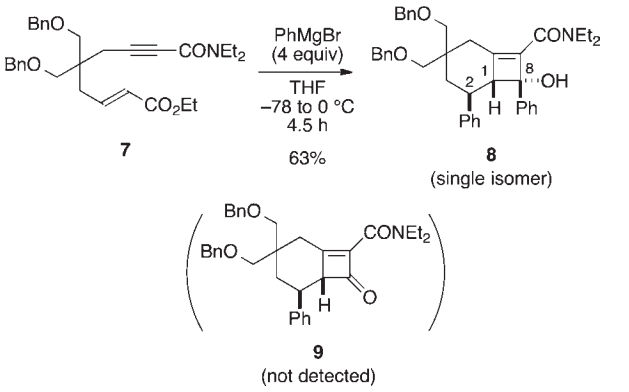


Scheme 2. Efficiency in Synthesis



simply treated with excess phenylmagnesium bromide,[5] the starting material disappeared and a considerable amount of a new product was recovered (Scheme 3). The spectroscopic properties of this product suggested it to be bicyclic cyclobutenol **8**, which corresponds to the aforementioned product **6** in Scheme 1.[6] No other isomeric products including cyclobutenone **9** were observed in the crude reaction mixture by ^{1}H NMR spectroscopy. Although the stereochemistry at the C1 and C2 positions of **8** could be assigned by the coupling constant between these hydrogens (J = 10.2 Hz) from the ^{1}H NMR spectrum, the 1,8-relationship in **8** was equivocal. The unambiguous

Scheme 3



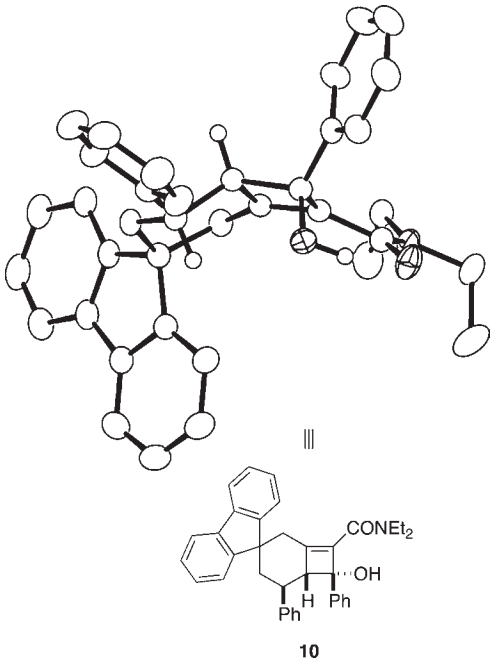


Figure 1. ORTEP drawing of **10**.

structure was ultimately confirmed by X-ray crystallography of fluorene analogue **10** (Table 1, entry 9), whose ORTEP drawing is shown in Figure 1.[7]

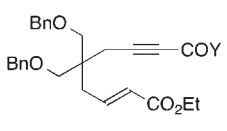
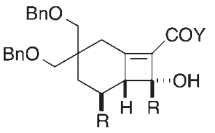
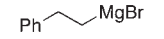
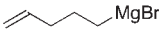
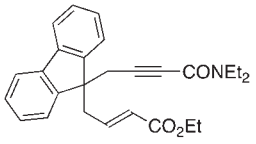
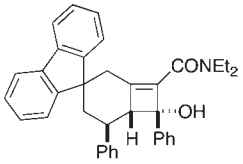
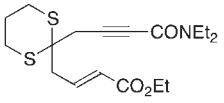
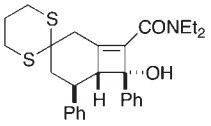
Additional cyclobutenols prepared by this method are shown in Table 1. Primary alkyl Grignard reagents such as butyl-, octyl-, phenethyl-, and 4-pentenylmagnesium bromides always gave the desired products **14**–**17** as a single stereoisomer (Table 1, entries 1–4). The more sterically hindered isopropyl Grignard reagent was equally effective, giving **18** in good yield (Table 1, entry 5). Aryl Grignard reagents also took part in the cyclization to give **8** and **19** (Table 1, entries 6 and 7). When diester **11** was used, the

(5) The 1,4-addition of Grignard reagent to a 2-alkenoate without copper catalyst has been precedented: Munch-Petersen, J. *Org. Synth.* **1961**, *41*, 60–64. In *Organic Syntheses*; Baumgarten, H. E., Ed.; John Wiley & Sons: New York, 1973; Coll. Vol. 5, pp 762–766. When 2 equiv of Grignard reagent was used instead, ketone **9** and product **8** could not be isolated. Even if a copper catalyst (10 mol% to **7**) was added with 4 equiv of PhMgBr to promote the first conjugate addition, unexpectedly, the yield of **8** decreased to 28% (CuI) or 30% (CuCN).

(6) Recent reports on the synthesis of bicyclo[4.2.0]octenes: (a) Fürstner, A.; Schlecker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277–4279. (b) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892–897. (c) Li, H.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. *Org. Lett.* **2010**, *12*, 3780–3783. (d) Commandeur, M.; Commandeur, C.; De Paolis, M.; Edmunds, A. J. F.; Maienfisch, P.; Ghosez, L. *Tetrahedron Lett.* **2009**, *50*, 3359–3362. (e) Korotvička, A.; Hybelbauerová, S.; Kotora, M. *Synlett* **2009**, 2445–2448. (f) Koldobskii, A. B.; Solodova, E. V.; Godovikov, I. A.; Kalinin, V. N. *Tetrahedron* **2008**, *64*, 9555–9560. (g) Oh, C. H.; Kim, A. *Synlett* **2008**, 777–781.

(7) The data have been deposited at the Cambridge Crystallographic Data Centre (file no. CCDC 762549) and can be obtained free of charge via www. ccdc.cam.ac.uk/data_request/cif.

Table 1. Synthesis of Various Bicyclic Cyclobutenols According to Scheme 3

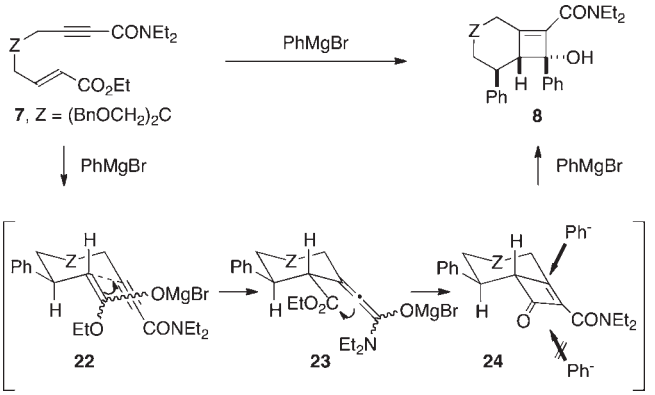
entry	substrate	RMgX	product (isolated yield)
			
1	**7**, Y = Et_2N	BuMgBr	**14** (65%)
2		$C_8H_{17}MgBr$	**15** (53%)
3			**16** (65%)
4[a]			**17** (63%)
5[b]		*i*-PrMgCl	**18** (72%)
6		PhMgBr	**8** (63%)
7		4-MeO-C_6H_4MgBr	**19** (69%)
8	**11**, Y = *t*-BuO	PhMgBr	**20** (79%)
9	 **12**	PhMgBr	 **10** (57%)
10	 **13**	PhMgBr	 **21** (57%)

[a] Grignard reagent (3.6 equiv) was used. [b] Grignard reagent (6.2 equiv) was used.

first intermolecular addition of the Grignard reagent occurred exclusively at the olefinic bond to give similar product **20** as above.[8] Thus, discrimination between olefinic and acetylenic esters is possible in the conjugate addition of Grignard reagents. In Table 1, entries 9 and 10 show substrates having different tether substituents including dithiane.[9,10] The stereochemistry of bicyclic cyclobutenols in Table 1 was assigned on the basis of that determined for **10**.

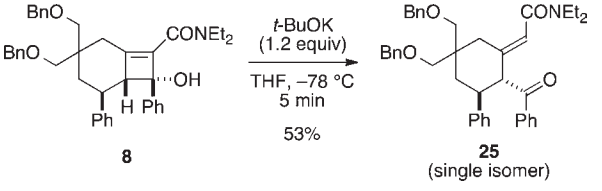
The proposed stereochemical course of the reaction is shown in Scheme 4. Conjugate addition of the Grignard reagent to the olefinic ester in **7** leads to enolate **22**, wherein the small olefinic hydrogen and the large Ph group occupy the axial and equatorial positions, respectively, in a chair-like alignment. From this conformation, the ring closure occurs to generate allenolate **23**, which undergoes an intramolecular addition to the ester carbonyl group to give cyclobutenone **24**. Finally, stereoselective 1,2-addition of the Grignard reagent to **24** from its convex face furnishes cyclobutenol **8** with the specified stereochemistry. It should be emphasized that overall, this reaction creates four new carbon−carbon bonds in a stereoselective manner, incorporating three components in one pot.[11]

Scheme 4. Proposed Stereochemical Course to Bicyclo-[4.2.0]octenols



The bicyclic cyclobutenols described above appear to be susceptible to a retro-aldol reaction, as evidenced by the fact that **8** collapsed to cyclohexane **25** upon treatment with *t*-BuOK in THF even at −78 °C (Scheme 5).[12] Thus, this transformation offers a stereoselective route to synthesize polysubstituted cyclohexane derivatives.

Scheme 5



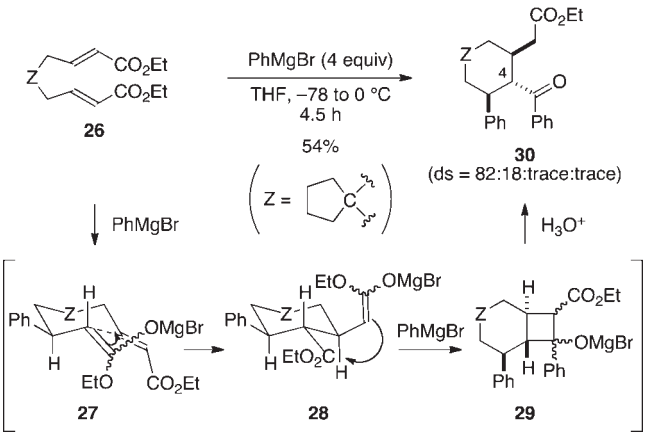
This sequence turned out to be the major pathway when alkadienediester was used instead of alkenynediester as a substrate, as shown in Scheme 6. Following the addition of the Grignard reagent to alkadienedioate **26**, a diolefinic counterpart of **11**, the expected cyclobutanol resulting from the hydrolytic workup of **29** was not isolated.[13,14] Instead, **29** apparently suffered the retro-aldol reaction as

(8) The reaction of the corresponding diethyl ester instead of **11** failed, affording a complex mixture of products.

(9) For reviews on dithianes, see: (a) Seebach, D. *Synthesis* **1969**, 17–36. (b) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357–402. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258. (d) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643–7677. (e) Kolb, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp 2983−2989. (f) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147–6212. For a recent example of conversion of dithianes, see: (g) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577–7581.

(10) As the cyclization of some substrates having a non- or mono-substituted tether was unsuccessful, the geminal disubstitution to the tether portion appears essential in this reaction. For a review on the geminal-disubstituent effect, see: (a) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766. For the same effect by dithiane, see: (b) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577–7581. In addition, similar substrates with a *gem*-disubstituted ethylene tether did not give the corresponding bicyclo[3.2.0]heptenols.

Scheme 6. Cyclohexanes Prepared from Alkadienedioate and Grignard Reagent



demonstrated in Scheme 5, giving ketoester **30** directly with good diastereoselectivity. The depicted relative stereochemistry of major isomer **30** was deduced on the basis of the ^{1}H NMR coupling constant for the hydrogen at the 4-position (triplet, J = 10.8 Hz).

In conclusion, four consecutive nucleophilic additions to alkenynedioic acid derivatives, incorporating two molecules of Grignard reagent, proceeded in one pot to give stereodefined bicyclo[4.2.0]octenols. Further investigations into this new type of tandem cyclization as well as synthetic applications of the products are now in progress.

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Supporting Information Available. Experimental procedures and spectroscopic properties for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) For reviews on multicomponent reactions, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169–6193. (c) Arndtsen, B. A. *Chem.—Eur. J.* **2009**, *15*, 302–313. (d) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (e) González-López, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164–189. (f) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (g) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (h) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907. (i) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (j) von Wangelin, A. J.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 4286–4294. (k) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (l) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831–844.

(12) For ring opening of a 4-hydroxy-1-cyclobutene-1-carboxylate with base, see: (a) Mislin, G. L.; Miesch, M. *J. Org. Chem.* **2003**, *68*, 433–441. (b) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485–3488.

(13) The cyclization of 8-oxo-2-alkenoates involving the intermediates similar to **27** and **28** has been reported; see: (a) Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667–4672. (b) Takasu, K.; Misawa, K.; Ihara, M. *Tetrahedron Lett.* **2001**, *42*, 8489–8491.

(14) *trans*-Fused bicyclo[4.2.0]octanes are allowed structures: (a) Laureillard, J. *Tetrahedron* **1979**, *35*, 1633–1648. (b) Meinwald, J.; Tufariello, J. J.; Hurst, J. J. *J. Org. Chem.* **1964**, *29*, 2914–2919.

The authors declare no competing financial interest.