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A New Strategy for Cyclopentenone Synthesis

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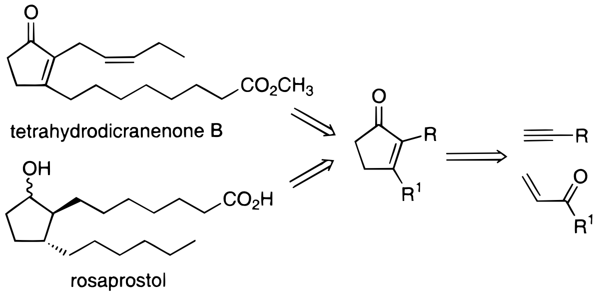
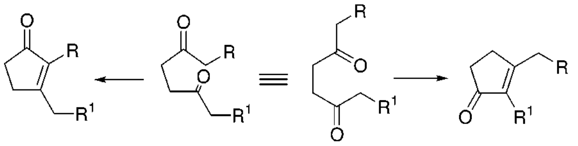
ABSTRACT



A new strategy for the synthesis of 2,3-disubstituted cyclopentenones emerges from two key reactions—the ruthenium-catalyzed three-component coupling of an equivalent of HBr, an alkyne, and a vinyl ketone and the Ni–Cr Barbier type reaction. As a result, these important structures are readily accessed from an alkyne and a vinyl ketone (which derive directly from carboxylic acids). Syntheses of tetrahydrodicranenone B and rosaprostol illustrate the new strategy.

The vast importance of cyclopentyl compounds has led to numerous methods for their synthesis.[1,2] Nevertheless, new strategies provide enhanced opportunities for increasing efficiency. Cyclopentenones are particularly useful because of the versatility of the functionality. The classical method for their synthesis involves the intramolecular aldol reaction of a suitable 1,5-diketone. Examination of eq 1 makes the



(1)

major issue immediately apparent—chemoselectivity. Two possible aldol products are equally accessible. We report a new strategy to avoid this ambiguity which we developed in the context of a synthesis of tetrahydrodicranenone B (**1**), a cyclopentenone fatty acid isolated from the Japanese moss *Leucobryum scabrum* which shows antimicrobial and antihypertensive properties.[3,4] A facile synthesis of rosaprostol, a clinically important antiulcer agent, also emerged from this chemistry.[5,6]

Scheme 1 illustrates the strategic concept which derives from the known oxidative rearrangement of tertiary allylic

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(1) For a few recent references, see: Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7026. Sturla, S. J.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 5547. Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. Yamamoto, Y.; Matsumi, D.; Hattori, R.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 3224. Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 2178. Taber, D. F.; Yu, H.; Incarvito, C. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 13285. Sugihara, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **1998**, *120*, 10782. Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett.* **1998**, *39*, 7637, 7641.

(2) For some reviews, see: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. Geis, O.; Schmalz, H. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164. Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier: New York, 1995; Vol. 12, p 703. Taber, D. F. *Methods of Organic Chemistry*; Helmchen, G., Ed.; Georg Thiem Verlag: Stuttgart, 1995; Vol. E 21, p 1127. Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.

(3) Ichikawa, T.; Namikawa, M.; Yamada, K.; Sakai, K.; Kondo, K. *Tetrahedron Lett.* **1983**, *24*, 3337.

(4) For syntheses, see: Sakai, K.; Fujimoto, T.; Yamashita, M.; Kondo, K. *Tetrahedron Lett.* **1985**, *26*, 2089. Moody, C. J.; Roberts, S. M.; Toczek, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1292.

(5) Valcavi, U.; Caponi, R.; Brambilla, A.; Palmira, M.; Minoja, F.; Bernini, F.; Musanti, R.; Fumagalli, R. *Arzneim-Forsch* **1982**, *32*, 657. Foschi, D.; et al. *Prostaglandins Leukotrienes Med.* **1984**, *15*, 147.

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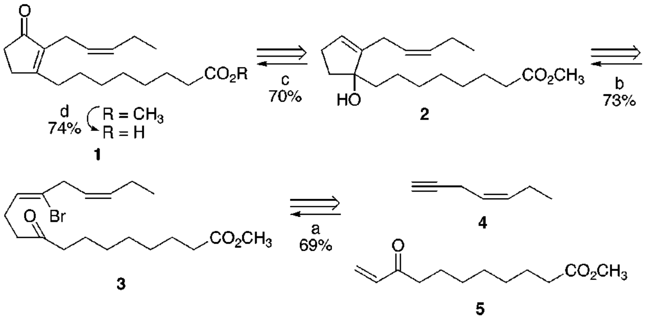
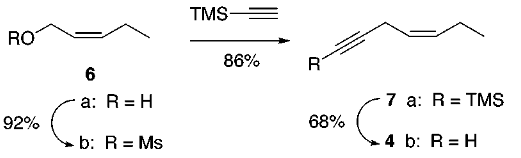
Scheme 1. Retrosynthetic Analysis and Synthesis of Tetrahydrodicranenone B (**1**)[a]



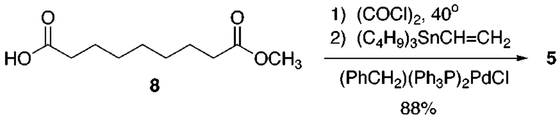
[a] (a) 10% $CpRu(CH_3CN)_3PF_6$, 15% $SnBr_4$, LiBr, CH_3COCH_3, 60 °C; (b) $CrCl_2$, $NiCl_2$, DMF, room temperature; (c) PDC, CH_2Cl_2, 0 °C; (d) LiOH, H_2O, dioxane, 60 °C.

alcohols.[7] A Barbier type reaction of *Z*-vinyl bromide **3** constitutes a ring-forming appraoch to the requisite allyl alcohol **2**. On the basis of a new ruthenium-catalyzed three-component coupling under development in these laboratories,[8] the alkyne **4** and the enone **5** become the starting materials.

The known enyne **4**[9] was derived as outlined in eq 2. The mesylate **6b** prepared from commercially available (*Z*)-2-penten-1-ol (**6a**) (MsCl, $(C_2H_5)_3N$, THF, 0 °C), underwent copper-mediated displacement with trimethylsilylacetylene (CuI, NaI, K_2CO_3, DMF, room temperature)[10] to give **7** in addition to the product of S_N2' displacement in a 3−9:1 ratio depending upon the amount of copper iodide. Desilylation (TBAF, HOAc, THF, room temperature) provided the known enyne **4**. The yield of this last step mainly reflects difficulties in isolation due to the volatility of the compound. The vinyl ketone **5** was prepared from azelaic acid monomethyl ester (**8**) via a Stille type cross-coupling[11] as shown in eq 3.



(2)



(3)

Scheme 1 outlines the synthesis of tetrahydrodicranenone B from the two subunits, **4** and **5**. Subjecting a 1:1 mixture of these two building blocks and lithium bromide to a two-component ruthenium−tin catalyst[12] in acetone at 60 °C gave a 4:1 mixture of the *Z* and *E* bromoalkenes (only the major (*Z*)-bromoalkene depicted). Despite little precedent for Barbier reactions mediated by chromous chloride-nickel chloride with ketones,[13,14] this intramolecular reaction proceeded very well with ketones under standard conditions to give the desired cyclopentenol **2**. PDC-promoted allylic rearrangement simultaneous with oxidation[7] produced the desired cyclopentenone as its ester, the hydrolysis of which gave the target **1**.

The facility of the sequence led us to develop this strategy for a synthesis of rosaprostol (**8**), an antiulcer drug marketed as the sodium salt under the name Rosal. It displays gastric antisecretory activity devoid of many side effects of other prostanoids.[5] Scheme 2 illustrates the retrosynthetic analysis. Since cyclopentanone **9** is a known precursor,[6] the corresponding cyclopentenone **10** represents a reasonable intermediate. Following the logic as outlined for tetrahydrodicranenone B, alkyne **13** and vinyl ketone **14** become the basic building blocks. Alkyne **13** is available by simple Fischer esterification of the corresponding commercially available 8-nonynoic acid. Known vinyl ketone **14**[15] is available from heptanoic acid via the Stille cross-coupling in identical fashion to the synthesis of vinyl ketone **5** (eq 3).

As shown in Scheme 2, the ruthenium-catalyzed three-component coupling proceeded in a fashion similar to that used previously to give a 70% yield of a 4:1 *Z*:*E* ratio of vinyl bromides (only the major *Z*-vinyl bromide **12** depicted.). Subjecting the mixture to the Ni−Cr-mediated Barbier type reaction gave a 71% isolated yield of allyl alcohol **11** whose oxidative rearrangement produced cyclopentenone **10** straightforwardly. Catalytic hydrogenation using Pd/C delivered a 3:1 *trans:cis* ratio of 2,3-disubstituted cyclopentanones. However, base hydrolysis of the ester was accompanied by equilibration to give only the *E* cyclopentanone−carboxylic acid. Sodium borohydride reduction as reported in the literature produced rosaprostol **8**.

The chemoselectivity exhibited in the ruthenium-catalyzed three-component coupling should make this a versatile

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[6] For syntheses, see: (a) Mikolajczyk, M.; Zurawinski, R. *J. Org. Chem.* **1998**, *63*, 8894. (b) Tanimori, S.; Kainuki, T.; Nakayama, M. *Biosci. Biotech. Biochem.* **1992**, *56*, 1807. (c) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175. (d) Valcavi, U.; Innocenti, S.; Bosone, E.; Farina, P.; Marotta, V.; Zabban, G. B. Eur. Pat. Appl. EP 155392; *Chem. Abstr.* **1986**, *104*, 168263C.

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[9] Billington, D. C.; Bladon, P.; Helps, I. M.; Pauson, P. L.; Thomson, W.; Willison, D. *J. Chem. Res.* **1988**, *10*, 2601.

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[11] For a representative procedure, see: Darwish, I. S.; Patel, C.; Miller, M. J. *J. Org. Chem.* **1993**, *58*, 6072. For a review, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998.

[12] For the ruthenium−acetonitrile complex, see: Gill, T. P.; Mann, K.R. *Organometallics* **1982**, *1*, 485.

[13] For a review, see: Cintas, P. *Synthesis* **1992**, 248.

[14] For an intramolecular example, see: Chen, X.-T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563. For a recent modification for reactions with ketones, see: Chen, C. *Synlett* **1998**, 1311.

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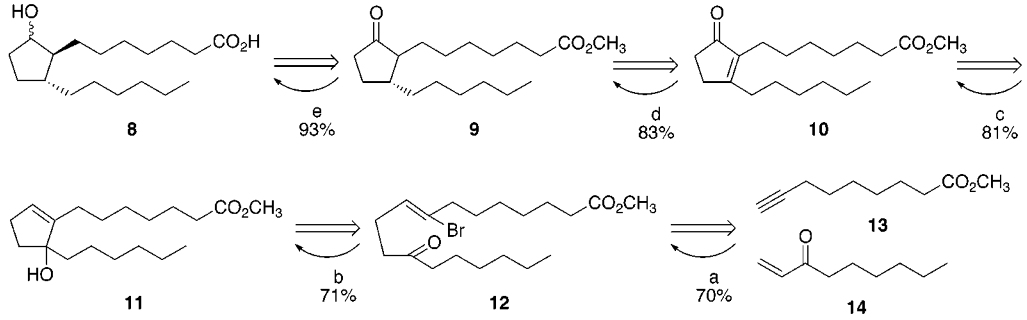
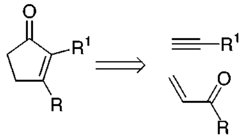
Scheme 2. Retrosynthetic Analysis and Synthesis of Rosaprostol (**8**)[a]



[a] (a) 10% $CpRu(CH_3CN)_3PF_6$, 15% $SnBr_4$, LiBr, CH_3COCH_3, 60 °C; (b) $CrCl_2$, $NiCl_2$, DMF, room temperature; (c) PDC, CH_2Cl_2, 0 °C; (d) H_2, Pd/C, CH_3OH, room temperature; (e) i. LiOH, H_2O, dioxane, 60 °C; ii. $NaBH_4$, CH_3OH, 0 °C.

approach to cyclopentenones. The synthesis of tetrahydrodicranenone B requires seven linear steps and 14% overall yield, but the yields have not been optimized. Rosaprostol also requires seven linear steps and proceeds in 31% overall yield. The ease of access of vinyl ketones from carboxylic acids[11,16] and alkynes makes this strategy particularly attractive. Retrosynthetically, 2,3-disubstituted cyclopentenones now can be envisioned to evolve as shown in eq 4.



(4)

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Supporting Information Available: Characterization data for **1**, **2**, **3**, **8**, **9**, **10**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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