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A Homo Diels–Alder Approach to Bicyclo[4.2.1]nonanes

Bin Ma and John K. Snyder*

Department of Chemistry, Boston University, 590 Commonwealth Ave., Boston, Massachusetts 02215

jsnyder@chem.bu.edu

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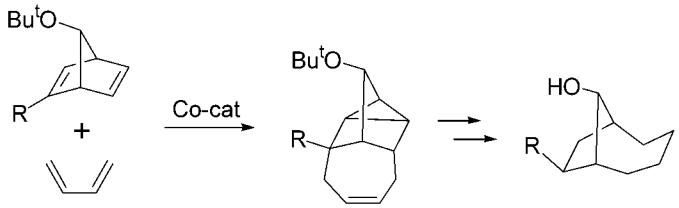
ABSTRACT



A new, high-yielding route to functionalized bicyclo[4.2.1]nonanes has been achieved utilizing homo Diels–Alder chemistry with subsequent Zeise's dimer-catalyzed opening of the cycloadduct.

The bicyclo[4.2.1]nonane skeleton has filled various roles in organic chemistry. Bicyclo[4.2.1]nona-9-one was first reported as an unanticipated product from the reaction of cyclopentanone with 1,4-bisdiazobutane.[1] Soon thereafter, bicyclo[4.2.1]nona-2,4,7-trienes appeared as the equally unexpected products from the acylation of cyclooctatetraene dianion[2] and, in the late 1960s and early 1970s, became enmeshed in the studies of aromaticity,[3] π-participation,[4] anti-Bredt olefins,[5] and various skeletal rearrangements.[6] The need for models to support these investigations soon led to an efficient preparation of bicyclo[4.2.1]nona-2,4,7-trien-9-one reported by Shechter.[7] Other routes to bicyclo[4.2.1]nonanes subsequently appeared.[8] Interest in this core structure was rekindled by the discovery of the antitumor mediterraneols in 1985,[9] which bore this bicyclic core rare to natural products. Various approaches to this system have since been reported that greatly increase the functional diversity of substituents on the core structure.[10]

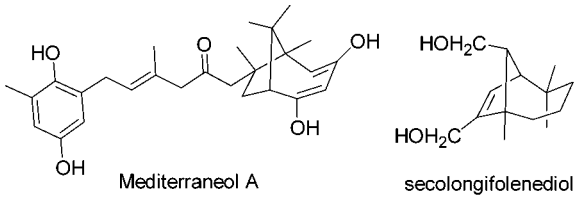


Figure 1. Natural products with the bicyclo[4.2.1]nonane core.

We have investigated the transition metal-catalyzed [4 + 2 + 2] homo Diels−Alder reactions of norbornadienes **1** with 1,3-butadienes and the opening of the dihydrocycloadducts

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(3) Gillissen, H. M. J.; Buck, H. M. *J. Org. Chem.* **1982**, *47*, 5124.
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(6) (a) Kende, A. S.; Bogard, T. L. *Tetrahedron Lett.* **1967**, 3383. (b) Paquette, L. A.; Wingard, R. E., Jr.; Meisinger, R. H. *J. Am. Chem. Soc.* **1971**, *93*, 1047. (c) Berson, J. A.; Boettcher, R. R.; Vollmer, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 1540. (d) Kurabayashi, K.; Mukai, T. *Tetrahedron Lett.* **1972**, 1049. (e) Paquette, L. A.; Meisinger, R. H.; Wingard, R. E., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 2155. (f) Kurabayashi, K.; Makai, T. *Tetrahedron Lett.* **1972**, 1049.
(7) Antkowiak, T. A.; Sanders, D. C.; Trimitsis, G. B.; Press: J. B.; Shechter, H. *J. Am. Chem. Soc.* **1972**, *94*, 5366.
(8) (a) Jefford, C. W.; Burger, U.; Delay, F. *Helv. Chim. Acta* **1973**, *56*, 1083. (b) Kraus, W.; Rothenwohrer, W.; Sadlo, H.; Klein, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 641. (c) Onoue, H.; Maritani, I.; Murahashi, S.-I. *Tetrahedron Lett.* **1973**, 121. (d) Boerth, D. W.; Van-Catledge, F. A. *J. Org. Chem.* **1975**, *40*, 3319. (e) Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 451. (f) Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 1563. (g) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670. (h) Trahanovsky, W. S.; Surber, B. W.; Wilkes, M. C.; Preckel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779.

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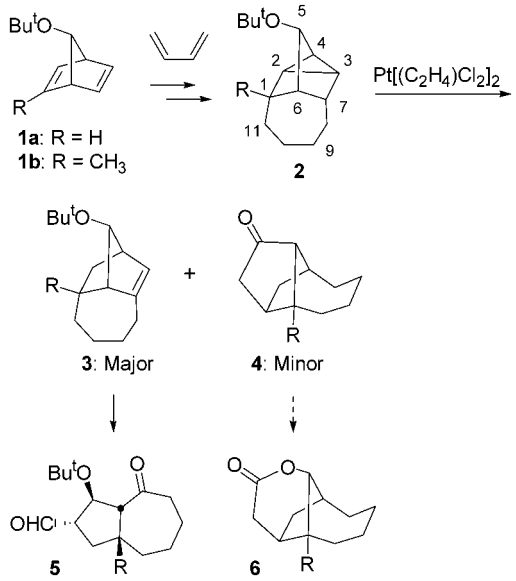
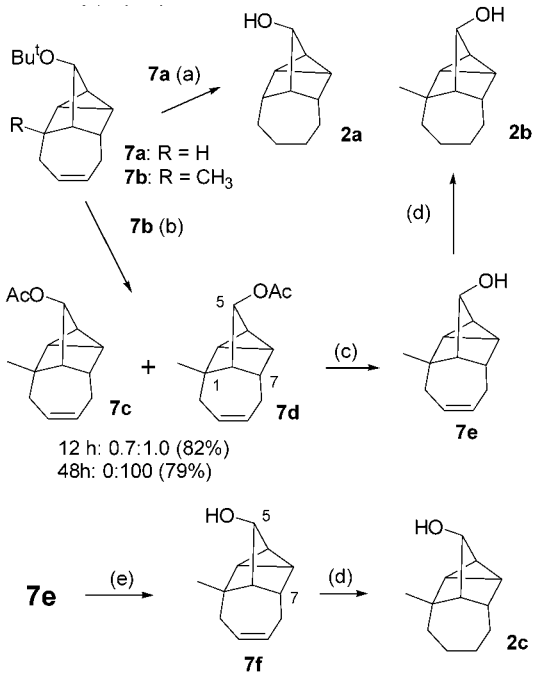
Scheme 1



2 to the bicyclo[5.3.0]decane systems (Scheme 1).[11] Recently, we reported that Zeise's dimer opening of the cycloadducts gives primarily tricyclo[6.2.1.0^{3,9}]un-dec-2-enes **3** by a mechanism proposed to proceed through Pt-insertion into the bottom face of the cyclopropane ring.[11b] Ozonolysis then gave the bicyclo[5.3.0]decanes **5**. In some of these ring openings, varying amounts of byproducts identified as tricyclo[5.4.0.0^{3,7}]undecan-5-ones **4** were found (up to 36%), and it was suggested that these arose from an oxygen-directed insertion of the platinum into the top cyclopropane bond syn to the *tert*-butoxy substituent. These byproducts were intriguing since Baeyer−Villiger oxidation would produce lactones **6**, which incorporate the bicyclo[4.2.1]nonane skeleton. If oxygen-directed Pt-insertion into the top face of the cyclopropane ring was responsible for the formation of **4**, enhancing the coordination of Zeise's dimer with this oxygen should greatly favor the production of **4** at the expense of **3** in the cyclopropane ring opening. Thus, removal of the *tert*-butyl group and subjecting the alcohol to Zeise's dimer should result in the formation of ketones **4** in excellent yields. We now report our preliminary results of this approach to bicyclo[4.2.1]nonanes.

The cobalt-catalyzed homo Diels−Alder reactions of 7-*tert*-butoxynorbornadiene[12] (**1a**) and *syn*-7-*tert*-butoxy-2-methylnorbornadiene (**1b**)[13] with 1,3-butadiene proceeded in near quantitative yields on a gram scale with the newly formulated catalyst system CoI_2/dppe/Zn/ZnI_2 (1:1:1:3, 5 mol % in Co)[14] to produce **7a** and **7b** (Scheme 2).[15] The *tert*-butyl group of **7a** was removed by treatment with H_2SO_4 (10%) in CH_2Cl_2 followed by hydrogenation to give **2a**. Removal of the *tert*-butyl group of **7b** required 10% H_2SO_4/HOAc. The anti acetate **7d** was the sole product obtained after 48 h. The stereochemistry was established by NOE studies: saturation of H-5 resulted in an enhancement of the C1 methyl singlet. When the acid exposure was limited to 12 h, an inseparable 0.7:1 mixture of syn:anti acetates (**7c**:**7d**) was obtained. Basic (LiOH) hydrolysis of **7d** gave the anti alcohol **7e** with hydrogenation then providing saturated anti alcohol **2b**. The syn alcohol **2c** could be prepared with exclusive stereoselectivity by oxidation of **7e** (PCC) followed by LAH reduction (97%, two steps) and hydrogenation. The stereochemical identity of **7f** was confirmed by NOE experiments with the saturation of H-5 producing an enhancement of the H-7 resonance.

Scheme 2[a]



[a] Reaction conditions: (a) 10% H_2SO_4/CH_2Cl_2 (80%), then H_2, Pd−C (95%); (b) H_2SO_4/HOAc; (c) LiOH (94%); (d) H_2, Pd−C (95%); (e) PCC, then LAH (97%, two steps).

Treatment of these apical alcohols **2a**−**c** with Zeise's dimer (10 mol %) then proceeded in refluxing toluene in

(9) (a) Francisco, C.; Banaigs, B.; Valls, R.; Codomier, L. *Tetrahedron Lett.* **1985**, *26*, 2629. (b) Francisco, C.; Banaigs, B.; Teste, J.; Cave, A. *J. Org. Chem.* **1986**, *51*, 1115.

(10) (a) Jung, M. E.; Kaas, S. M. *Tetrahedron Lett.* **1989**, *30*, 641. (b) MacCorquodale, F.; Walton, J. C. *J. Chem. Soc,. Perkin Trans. 1* **1989**, 347. (c) Kakiuchi, K.; Fukunaga, K.; Matsuo, F.; Ohnishi, Y.; Tobe, Y. *J. Org. Chem.* **1991**, *56*, 6742. (d) Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122. (e) Rigby, J. H.; Aleeq, H. S.; Charles, N. R.; Henshilwood, J. A.; Short, K. M.; Sugathapala, P. M. *Tetrahedron* **1993**, *49*, 5495. (f) Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851. (g) Frontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. *Tetrahedron* **1998**, *54*, 1272. (h) Srikrishna, A.; Ramachary, D. B. *Tetrahedron Lett.* **1999**, *40*, 1605.

(11) (a) Chen, Y.; Kiattansakul; Ma, B.; Snyder, J. K. *J. Org. Chem.* **2001**, *66*, 6932. (b) Chen, Y.; Snyder, J. K. *J. Org. Chem.* **2001**, *66*, 6943.

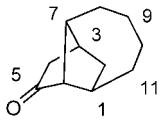
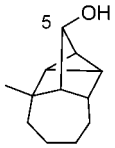
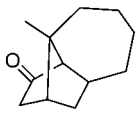
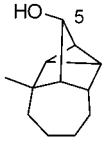
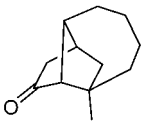
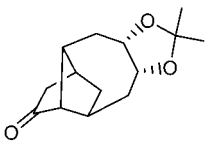
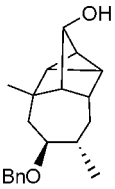
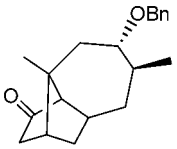
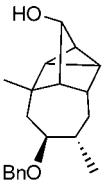
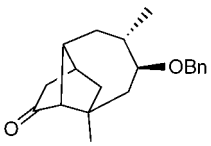
(12) (a) Story, P. R. *J. Org. Chem.* **1961**, *26*, 287. (b) Story, P. R.; Fahrenholtz, S. R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 151.

(13) Supporting Material of: Chen, Y.; Snyder, J. K. *J. Org. Chem.* **1998**, *63*, 2060.

(14) Ma, B.; Snyder, J. K., to be submitted to *Organometallics*.

(15) All new compounds were fully characterized by ^{1}H and ^{13}C NMR and HRMS (see Supporting Information).

Table 1. Zeise's Dimer-Catalyzed Opening of **2**[a]

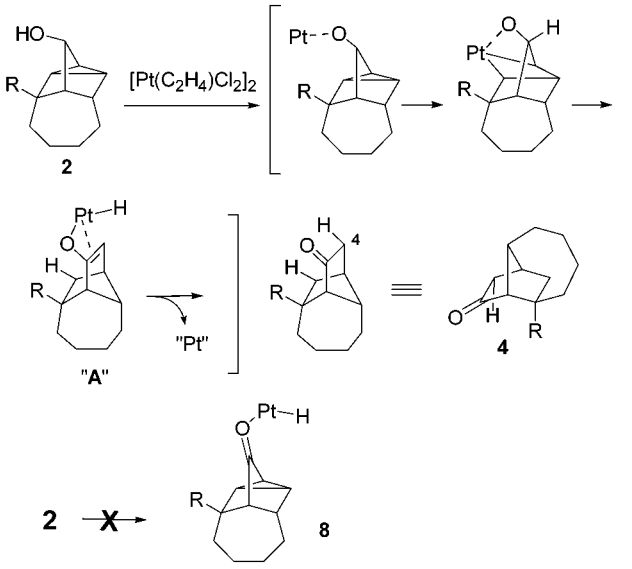
entry:**2**	substrate	product	yield
1: **2a**		 **4a**	97%
2: **2b**		 **4b**	99%
3: **2c**		 **4c**	99%
4: **2d**		 **4d**	99%
5: **2e**		 **4e**	98%
6: **2f**		 **4f**	98%
7: **2g**		-	-
8: **2h**		-	-

[a] All reactions in refluxing toluene, 0.1 M in **2**, 10 mol % $[Pt(C_2H_4)Cl_2]_2$.

excellent yields (97−99%) to give the corresponding tricycloundecanones **4a**−**c** (Table 1, entries 1−3). Reduction of the amount of catalyst to 5 mol % significantly retarded the reaction. Of particular note is the ability to direct the Pt-opening to either of the topside cyclopropane bonds by adjusting the stereochemistry of the C5 hydroxyl group (entries 2 and 3).

This Pt-promoted cyclopropane opening conceivably proceeds by hydroxyl-directed Pt(II)-insertion into the top face

Scheme 3

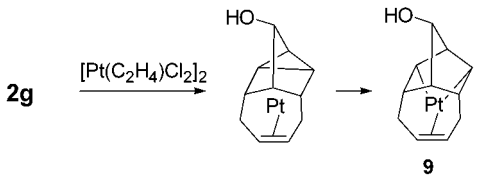


of the cyclopropane followed by hydrogen transfer to give the platinum enolate "**A**", which then tautomerizes to the observed ketones **4** with release of Pt(II) (Scheme 3), as previously suggested.[11b] In support of this mechanism, when 5-^{2}H **2c** was subjected to Zeise's dimer opening, all of the deuterium label was transferred to the C4 endo position.

The production of **4b** and **4c** from stereoisomers **2b** and **2c**, respectively, rules out initial Pt-insertion into the carbinol C−H bond or the intermediacy of the ketone **8**, which would be a common intermediate from both the syn and anti alcohols. The parent ketone (R = H) itself also proved to be unreactive toward Zeise's dimer.

If the alkene subunit of the original cycloadduct **2g** was not removed, no cyclopropane-opened product could be detected (Table 1, entry 7). A similar failure to turn over the Pt-catalyst was noted in Zeise's dimer-catalyzed opening of 5-*tert*-butoxycycloadduct **7a** retaining the C9−C10 double bond.[16] In these cases, Pt-insertion is presumably directed to the bottom face of the cyclopropane by prior olefin exchange,[17] forming a stable Pt-complex **9** with the olefin serving as a Pt-ligand, preventing turnover (Scheme 4).

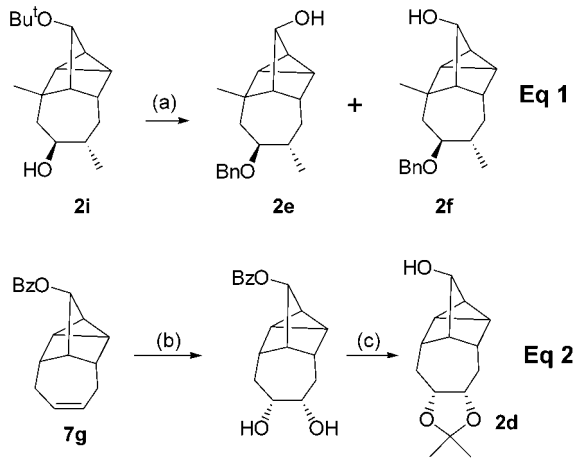
Scheme 4



The C9−C10 double bond of the original homo Diels−Alder cycloadducts can also be readily hydroborated to form

(16) Chen, Y. Ph.D. Dissertation, Boston University, Boston, MA, 1999.
(17) For reviews: (a) Puddephatt, R. J. *Coord. Chem. Rev.* **1980**, *33*, 149. (b) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241.

Scheme 5[a]



[a] Reaction conditions. (a) (i) $Cl_3CC(NH)OBn$, TfOH; (ii) H_2SO_4/HOAc, rt, then LiOH (87%, two steps, **2e**:**2f** = 1:1). (b) OsO_4, NMO (83%). (c) $(MeO)_2CMe_2$, *p*-TsOH (98%), then LiOH (97%).

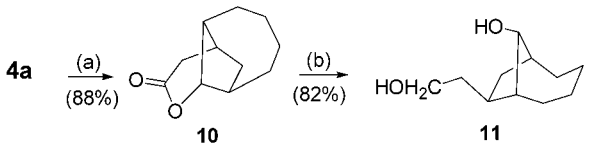
alcohol functionalities in the seven-membered ring. Benzylation of alcohol **2i**[11b] followed by removal of the *tert*-butyl group (H_2SO_4/HOAc) with basic workup (LiOH) gave a separable mixture of alcohols **2e** and **2f** (1:1, Scheme 5, eq 1). Routine transformations of known benzoate **7g**[11a] produced acetonide **2d** (Scheme 5, eq 2).

The hydroxyl-directed, Pt-catalyzed cyclopropane openings of these compounds were also successful (Table 1, entries 4−6). These tricyclic ketones **4** all bear the tricyclo[5.4.0.0^{3,7}]-undecane skeleton found in natural products such as longifolene[18] and related structures such as pseudolongicamphor[19] and culmarin.[20]

In contrast to the high stereoselectivity observed in the hydroborations of cycloadducts **7a** and **7b**,[12b,21] epoxidation of **7a** gave a nearly equal mixture of endo and exo epoxides **2h** (Table 1, entry 8), which were difficult to separate.

(18) For a review of longifolene: Dev, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag: New York, 1981; Vol. 40, p 49.
(19) Suryawanshi, S. N.; Nayak, U. R. *Tetrahedron Lett.* **1977**, 2619.
(20) Barton, D. H. R.; Werstuik, N. H. *J. Chem. Soc. C* **1968**, 148.

Scheme 6[a]



[a] Reaction conditions: (a) *m*-CPBA, $NaHCO_3$; (b) LAH.

Treatment of the mixture of epoxides **2h** with Zeise's dimer resulted in an intractable mixture of numerous products, with cyclopropyl hydrogens still clearly visible in the NMR spectrum of the crude product mixture, though no starting material remained. Platinum(II) has been reported to insert into epoxides,[22] so alternative pathways exist that could lead to the observed mixture of products.

With the tricycloundecanones in hand, Baeyer−Villiger oxidations of **4a** were examined in order to complete formation of a bicyclo[4.2.1]nonane. Under basic conditions, the oxidation proceeded uneventfully to give the corresponding lactone **10** in good yield (88%) as the sole detectable regioisomer (Scheme 4). Bicyclo[4.2.1]nonane lactone **10** was then opened to bicyclo[4.2.1]nonanediol **11** by reduction with LAH.

In summary, a new, high-yielding route to functionalized bicyclo[4.2.1]nonanes has been achieved utilizing homo Diels−Alder chemistry with subsequent Zeise's dimer-catalyzed opening of the cycloadduct.

Acknowledgment. This material is based upon work supported by the National Science Foundation under Grant CHE-0092061.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds **2a**−**f**, **4b**,**d**−**f**, **7d**−**f**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.
(22) Than, A. K.; Ferguson, G.; Lough, A. J.; Puddephatt, R. J. *Angew. Chem.* **1989**, *101*, 765.