ORGANIC LETTERS

2000
Vol. 2, No. 26
4225−4228

Cross-Coupling of Highly Pyramidalized Alkenes: A Straightforward Access to Functionalized Tetrasecododecahedradienes

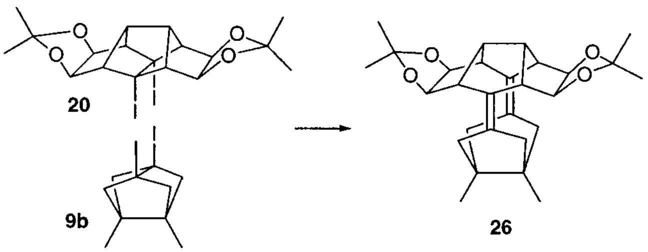
Pelayo Camps,* Xavier Pujol, and Santiago Vázquez

Laboratori de Química Farmacèutica, Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal 643, Barcelona, E-08028, Spain

camps@farmacia.far.ub.es

Received October 26, 2000

ABSTRACT



The synthesis and chemical trapping of a highly pyramidalized pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{4,9}]dodec-8-ene containing ketal functions is reported. Its cross-coupling reaction with 3,7-dimethyltricyclo[3.3.0.0^{3,7}]oct-1(5)-ene followed by a [2 + 2] retrocycloaddition reaction gives a straightforward access to functionalized tetrasecododecahedradienes.

The highly symmetrical hydrocarbon dodecahedrane, **7a**, remains a source of fascination to chemists.[1] Paquette et al.[2] and Prinzbach et al.[3] completed two landmark syntheses of **7a**. Moreover, Prinzbach et al. showed that suitably functionalized pagodanes could be transformed into substituted dodecahedranes in excellent yields.[4]

Nevertheless, completion of a convergent synthesis of **7a** still remains an attractive synthetic challenge.[5] To this end, we studied the dimerization of highly pyramidalized[6] alkene **2** which gave directly in low yield a mixture of the *syn*- and *anti*-diene dimers, **5** and **6**, in a ratio of about 1:1 that could

---

(1) (a) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: New York, 2000. (b) Forman, M. A. *The Chemist* **1996**, 3−8.

(2) (a) Ternansky, R. J.; Balogh, D. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4503−4504. (b) Paquette, L. A.; Ternansky, R. J.; Balogh, D. W.; Kentgen, G. *J. Am. Chem. Soc.* **1983**, *105*, 5446−5450. (c) Paquette, L. A. *Chem. Rev.* **1989**, *89*, 1051−1065. (d) Paquette, L. A. In *Cage Hydrocarbons*; Olah, G. A., Ed.; John Wiley & Sons: New York, 1990; pp 313−352.

(3) (a) Fessner, W. D.; Murty, B. A. R. C.; Worth, J.; Hunkler, D.; Fritz, H.; Prinzbach, H.; Roth, W. D.; Schleyer, P. v. R.; McEwen, A. B.; Maier, W. F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 452−454. (b) Fessner, W. D.; Prinzbach, H. In *Cage Hydrocarbons*; Olah, G. A., Ed.; John Wiley & Sons: New York, 1990; pp 353−405.

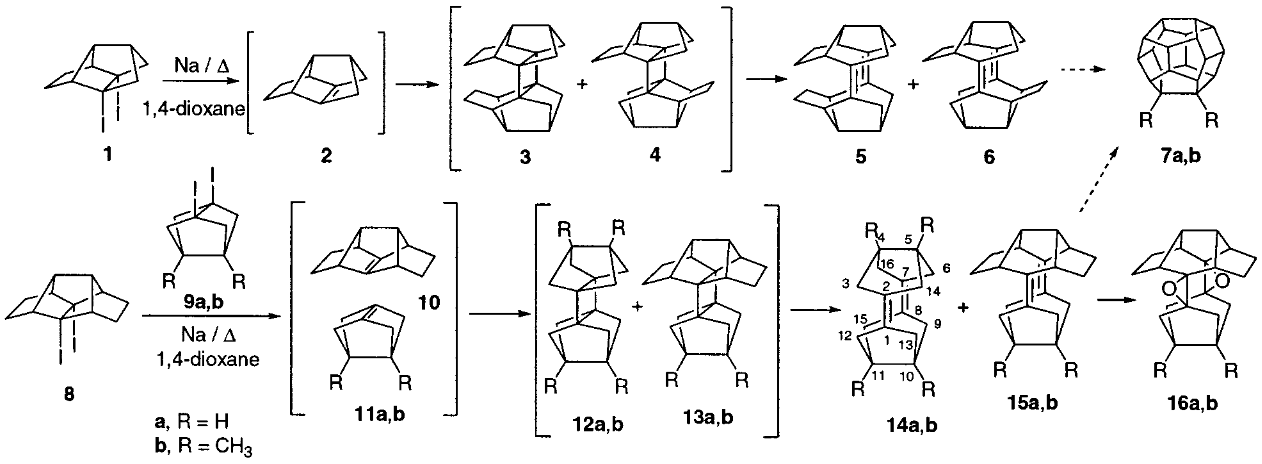
(4) (a) Prinzbach, H.; Weber, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2239−2257. (b) Weber, K.; Lutz, G.; Knothe, L.; Mortensen, J.; Heinze, J.; Prinzbach, H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1991−1997. (c) Melder, J. P.; Weber, K.; Weiler, A.; Sackers, E.; Fritz, H.; Hunkler, D.; Prinzbach, H. *Res. Chem. Intermed.* **1996**, *22*, 667−702. (d) Bertau, M.; Leonhardt, J.; Weiler, A.; Weber, K.; Prinzbach, H. *Chem. Eur. J.* **1996**, *2*, 570−579. (e) Pinkos, R.; Weiler, A.; Voss, T.; Weber, K.; Wahl, F.; Melder, J.-P.; Fritz, H.; Hunkler, D.; Prinzbach, H. *Liebigs Ann./Recueil* **1997**, 2069−2088. (f) Bertau, M.; Wahl, F.; Weiler, A.; Scheumann, K.; Wörth, J.; Keller, M.; Prinzbach, H. *Tetrahedron* **1997**, *53*, 10029−10040. (g) Scheumann, K.; Sackers, E.; Bertau, M.; Leonhardt, J.; Hunkler, D.; Fritz, H.; Wörth, J.; Prinzbach, H. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1195−1210. (h) Cross, R. J.; Saunders, M.; Prinzbach, H. *Org. Lett.* **1999**, *1*, 1479−1481. (i) Oβwald, T.; Keller, M.; Janiak, C.; Kolm, M.; Prinzbach, H. *Tetrahedron Lett.* **2000**, *41*, 1631−1635.

(5) For a review, see: (a) Eaton, P. E. *Tetrahedron* **1979**, *35*, 2189−2223. See also: (b) Paquette, L. A.; Farnham, W. P.; Ley, S. V. *J. Am. Chem. Soc.* **1975**, *97*, 7273−7279 (c) Deslongchamps, P.; Soucy, P. *Tetrahedron* **1981**, *37*, 4385−4390. (d) Roberts, W. P.; Shoham, G. *Tetrahedron Lett.* **1981**, *22*, 4895−4898. (e) Carceller, E.; García, M. L.; Serratosa, F.; Font-Altaba, M.; Solans, X. *Tetrahedron* **1987**, *43*, 2147−2156. (f) Fu, X.; Cook, J. M. *J. Org. Chem.* **1992**, *57*, 5121−5128.

(6) For an excellent review on pyramidalized alkenes, see: (a) Borden, W. T. *Chem. Rev.* **1989**, *89*, 1095−1109. See also: (b) Borden, W. T. *Synlett* **1996**, 711−719.

10.1021/ol0067843 CCC: $19.00

Scheme 1



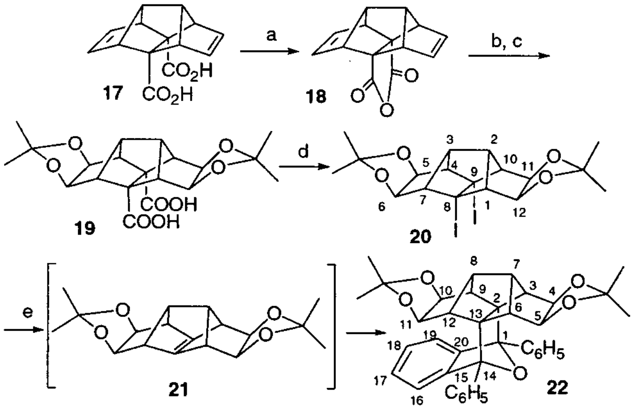
not be separated.[7] Dienes **5** and **6** were formed by [2 + 2] retrocycloaddition of the corresponding cyclobutane precursors **3** and **4**, respectively. Then, we carried out the first cross-coupling reaction of two highly pyramidalized alkenes. Reaction of the diiodides **9a** or **9b** and diiodide **8** with melted sodium afforded the corresponding tetrasecododecahedradienes **15a** and **15b** via the corresponding cyclobutane cross-products **13a** and **13b**. These dienes could not be separated from other hydrocarbons formed in the cross-coupling reaction due to their instability toward silica gel or aluminum oxide column chromatography and also the similar polarity of other components of the mixture, such as dienes **14a** or **14b** when an excess of **9a** or **9b** was used. When an excess of **8** was used, different $C_{24}H_{28}$ unidentified products, not separable from **15a** or **15b**, were also observed.[7a] Dienes **15a** and **15b** were converted to the corresponding diepoxides **16a** and **16b**, which were fully characterized, including an X-ray diffraction analysis of **16a** (Scheme 1).[7a]

In this Letter we wish to report the preparation of the functionalized highly pyramidalized alkene **21**, its trapping with 1,3-diphenylisobenzofuran (1,3-DPIBF), and its cross-coupling reaction with the known alkene **11b**, leading to the functionalized cyclobutane derivative **27** or diene **26**, depending on the reaction conditions. Further functional group manipulation from **27** led to the functionalized tetrasecododecahedradienetetrone **28**, via the cyclobutane derivatives **30** and **29**.

Compound **20** was prepared as shown in Scheme 2.

Anhydride **18**, obtained by reaction of the known diacid **17**[8] with acetic anhydride, was transformed into **19** in 84% global yield by a one-pot sequence that involved bis-dihydroxylation using *N*-methylmorpholine-*N*-oxide (NMO) and a catalytic amount of dipotassium osmate,[9] followed by acetonide formation with simultaneous anhydride hydrolysis by reaction with acetone and concentrated sulfuric acid. Iododecarboxylation of diacid **19** was carried out by reaction with iodosobenzene diacetate (IBDA) and iodine following the Moriarty[10] modification of the Suárez procedure.[11] Despite extensive experimentation, this reaction proceeded in moderate yield (33%), although diacid **19** was recovered in 49% yield, being reused without further purification.

Scheme 2[a]



[a] Reagents and conditions: (a) Ac_2O, reflux, 1 h, 86%; (b) NMO, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH/H_2O/acetone (1:1:1), room temperature, 23 h; (c) acetone, concentrated H_2SO_4, reflux, 18 h, 84% overall b, c; (d) IBDA, I_2, benzene, *hν*, 22 h, 33%; (e) 1,3-DPIBF, *t*-BuLi, THF, −78 °C, 30 min, 63%.

Reaction of **20** with *tert*-butyllithium in anhydrous THF at −78 °C in the presence of 1,3-diphenylisobenzofuran furnished, after silica gel column chromatography, the

---

[7] (a) Camps, P.; Font-Bardia, M.; Méndez, N.; Pérez, F.; Pujol, X.; Solans, X.; Vázquez, S.; Vilalta, M. *Tetrahedron* **1998**, *54*, 4679−4696. See also: (b) Camps, P.; Font-Bardia, M.; Pérez, F.; Solans, X.; Vázquez, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 912−914. (c) Camps, P.; Font-Bardia, M.; Pérez, F.; Solà, Ll.; Solans, X.; Vázquez, S. *Tetrahedron Lett.* **1996**, *37*, 8601−8604. (d) Camps, P.; Luque, F. J.; Orozco, M.; Pérez, F.; Vázquez, S. *Tetrahedron Lett.* **1996**, *37*, 8605−8608.

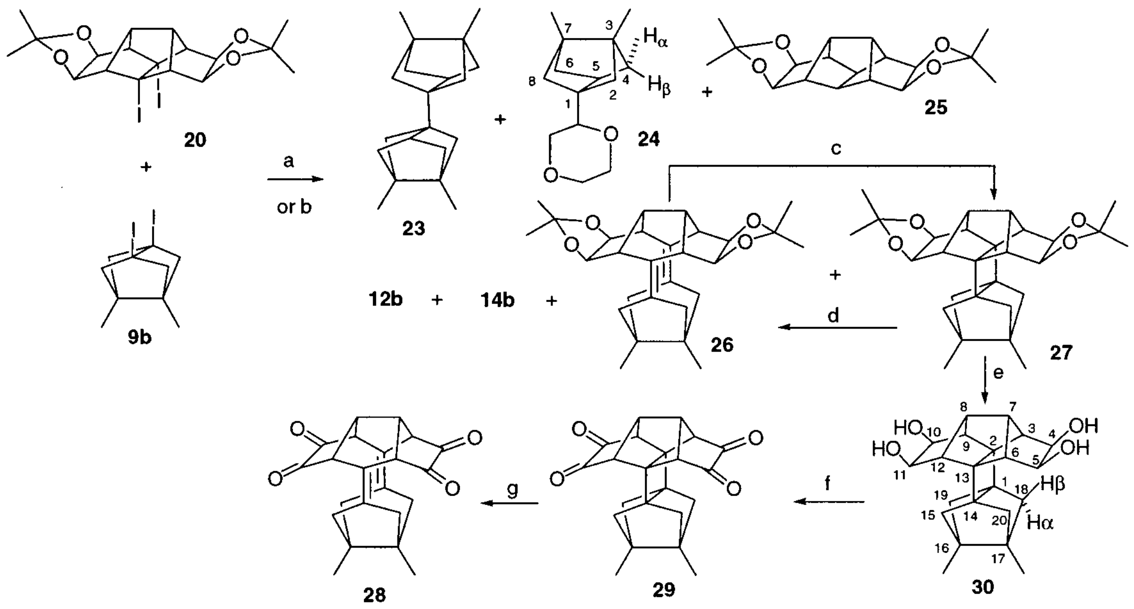
[8] Taylor, J.; Pelter, M. W.; Paquette, L. A. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 298−302.

[9] Haag, R.; Zuber, R.; Donon, S.; Lee, C.-H.; Noltemeyer, M.; Johnsen, K.; De Meijere, A. *J. Org. Chem.* **1998**, *63*, 2544−2547.

[10] Moriarty, R. M.; Khosrowshahi, J. S.; Dalecki, T. M. *J. Chem. Soc., Chem. Commun.* **1987**, 675−676.

[11] Concepción, J. I.; Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1986**, *51*, 402−404.

Scheme 3[a]



[a] Reagents and conditions: (a) Na, 1,4-dioxane, reflux 4 h; **23** (4.3%), **24** (1.2%), **25** (19%), **14b** (37%), **26** and **27** (55%); (b) Na (Hg), 1,4-dioxane, room temperature overnight; **23** (5.3%), **25** (48.5%) **12b** and **14b** (41.5%), **27** (52%) (yield of compounds **23**, **24**, **12b**, and **14b** was calculated from starting **9b**, while yield of **25**, **26**, and **27** was calculated from **20**, with a ratio **20**/**9b** of 1:3); (c) *hν*, cyclohexane, 6 h, quantitative yield; (d) 1,4-dioxane, reflux, 24 h, quantitative yield; (e) 2 N aq. HCl, methanol, 75 °C, 16 h, 99%; (f) DMSO, TFAA, dichloromethane, −60 °C, 2 h, then Et_3N, −60 °C, 90 min, 60%; (g) 1,4-dioxane, reflux, 3 h, quantitative yield.

expected Diels−Alder adduct **22**, derived from the highly pyramidalized alkene **21**, that was isolated in 63% yield.

Reaction of a mixture of diiodides **20** and **9b** in the molar ratio **20**/**9b** of 1:3 with excess of melted sodium in refluxing 1,4-dioxane for 4 h gave a mixture of products which could be separated by column chromatography (alumina, hexane/ethyl acetate mixtures) and were isolated in the following order of elution: dihydrodimer **23** (4.3% yield), diene dimer **14b** (37% yield), compound **24**, derived from alkene **11b** and 1,4-dioxane (1.2% yield), a mixture of the cross-coupled diene **26** and its isomeric cyclobutane precursor **27** in the approximate ratio of 4:1 (^{1}H NMR) (55% combined yield), and the reduction product **25** (19% yield). Under these conditions (great excess of **9b**) dimers of alkene **21** were not observed as been the case in the cross-coupling reactions of **8** and **9a** or **9b**. Contrary to our previous experience in the cross-coupling of alkenes **10** and **11a** or **11b**, whose diene or cyclobutane reaction product could not be isolated, the polarity differences among the products of the above reaction, due to the presence in several of them of acetal functions, allowed us to separate the polar cross-coupling products **26** and **27** from the less polar diene dimer **14b** and byproducts **23** and **24** and from the more polar product **25**.

When the cross-coupling reaction of **20** and **9b** was carried out using 0.45% sodium amalgam at room temperature, **27** was isolated in 52% yield, and the formation of **26** was not observed (Scheme 3). This observation suggests that the product initially formed in the cross-coupling of **11b** and **21** is the cyclobutane derivative **27** which under refluxing 1,4-dioxane is thermally transformed into diene **26**. Also, the formation of dimer **12b** was observed.

Isolation of compounds **23**, **24**, and **25** provides further evidence for the formation of radical intermediates in the [2 + 2] cycloaddition of highly pyramidalized alkenes.[12]

Irradiation of the mixture of **26** and **27** in a quartz reactor using a 125 W medium-pressure mercury lamp allowed us to obtain pure **27** in quantitative yield, after alumina column chromatography. Compound **27** was shown to be stable for extended periods of time at room temperature, although it was completely converted to **26** after being heated to reflux in a 1,4-dioxane solution for 24 h.

Acid hydrolysis of **27** gave quantitatively **30** which also shown to be stable for extended periods of time at room temperature. Swern oxidation of **30** gave the tetrone **29** in 60% isolated yield. We could purify **29** by column chromatography (alumina, hexane/ethyl acetate mixtures) and fully characterize it. However, **29** underwent slow [2 + 2] retrocycloaddition at room temperature to diene **28**, with complete conversion of **29** to **28** being observed after being heated to reflux in a 1,4-dioxane solution for 3 h.

It is worth noting the greater relative stability of the cyclobutane derivatives **27** and **30** when compared with **29**. This fact can be qualitatively understood on the basis of the strain energy involved in the cyclobutane opening of compounds **27** and **30** to their corresponding more spherical dienes. The strain energy due to the approach of the 4H/18H_β, 5H/20H_β, 10H/19H_β, and 11H/15H_β pairs of protons in the opened compounds may partially compensate the strain release associated with the opening of the cyclobutane. This type of interaction is not present in the conversion of **29** to

---

(12) Lukin, K.; Eaton, P. E. *J. Am. Chem. Soc.* **1995**, *117*, 7652−7656.

28 due to the absence of hydrogen atoms on the sp^2 hybridized C4, C5, C10, and C11 carbon atoms of these compounds.

Molecular mechanics calculations (MM2 program)[13] carried out on cyclobutane derivatives **27** and **29** and dienes **26** and **28** gave the formation enthalpies (ΔH_f, kcal/mol) and strain energies (E_{str}, kcal/mol) shown in Table 1. From these data, the following reaction enthalpies are obtained: ΔH(**27** → **26**) = −21.0 kcal/mol and ΔH(**29** → **28**) = −36.2 kcal/mol. As previously observed in related cases, the more exothermic reaction is the faster one.[7c,d]

Table 1. Formation Enthalpies and Strain Energies of **26**, **27**, **28**, and **29** (kcal/mol)

	27	**26**	**29**	**28**
ΔH_f	−108.4	−129.4	−34.2	−70.4
E_{str}	144.5	85.4	134.7	60.4

Also, from Table 1, the following strain energy differences can be obtained: ΔE_{str}(**27** → **26**) = −59.1 kcal/mol and ΔE_{str}(**29** → **28**) = −74.3 kcal/mol. These figures clearly reflect the greater strain release associated with the cyclobutane opening in compound **29** as compared with **27**, a fact that may be due to the increase in the steric interaction among the above-mentioned pairs of protons in the conversion of **27** to **26** that is not present in the conversion of **29** to **28**. In this case, the enthalpy difference for these reactions is equal to their strain energy difference. Similar situations had been previously observed in the pagodane series.[14]

All of the new compounds herein described have been fully characterized on the basis of their spectral data (IR, ^{1}H and ^{13}C NMR, COSY ^{1}H/^{1}H, COSY ^{1}H/^{13}C, NOE, and MS spectra) and elemental analyses. Worthy of note, in the MS spectra of dienes **26** and **28** the molecular ions are the base peaks; this is not the case for the cyclobutane derivatives **27** and **29**. This fact may be ascribed to the formation of highly stable cyclobutyl radical-cations similar to those described in the pagodane family.[15]

In conclusion, the cross-coupling of functionalized highly pyramidalized alkenes appears to be a valuable synthetic tool, a matter which is under study. Also, work is in progress to obtain the experimental enthalpies and the activation energies for the conversion of compounds **27** and **29** to the corresponding dienes.

Acknowledgment. Financial support from Comissionat per a Universitats i Recerca of the Generalitat de Catalunya (project 1999-SGR-00080) is gratefully acknowledged. We thank the Serveis Científico-Tècnics of the University of Barcelona and particularly Dr. M. Feliz and Dr. A. Linares for recording the NMR spectra and Ms. P. Domènech from the Centro de Investigación y Desarrollo (C.I.D.) (Barcelona, Spain) for carrying out the elemental analyses.

Supporting Information Available: Text giving experimental procedures and characterization data for the compounds. Torsional and bending parameters not parametrized for the 1,2-dicarbonyl groups of compounds **28** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0067843

---

(13) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127−8134.

(14) (a) Melder, J.-P.; Fritz, H.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 300−303. (b) Fessner, W.-D.; Murty, B. A. R. C.; Spurr, P. R.; Pinkos, R.; Melder, J.-P.; Fritz, H.; Prinzbach, H. *Chem. Ber.* **1992**, *125*, 1697−1717.

(15) (a) Spurr, P. R.; Murty, B. A. R. C.; Fessner, W.-D.; Prinzbach, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 455−456. (b) Gescheidt, G.; Prinzbach, H.; Davies, A. G.; Herges, R. *Acta Chem. Scand.* **1997**, *51*, 174−180. (b) Weiler, A.; Quennet, E.; Keller, M.; Exner, K.; Prinzbach, H. *Tetrahedron Lett.* **2000**, *41*, 4763−4767 and references therein.