Novel Pd(0)-Catalyzed Cyclization-Carbonylation of 2-Methyl-1-vinyl-5,6-heptadienyl Acetate : The Synthesis of (±)-Isoiridomyrmecin

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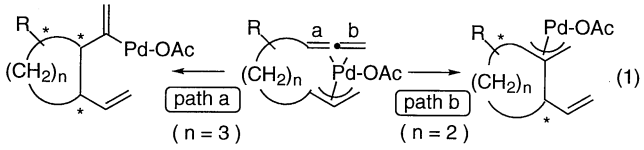
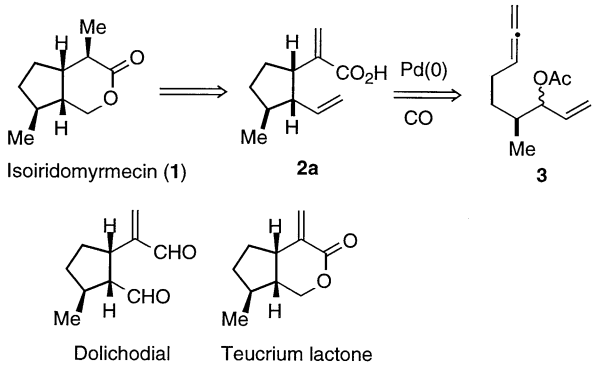
The Pd(0)-catalyzed cyclization-carbonylation of 2-methyl-1-vinyl-5,6-heptadienyl acetate regio- and stereoselectively gave an α-cyclopentylacrylic acid derivative which was applied to the synthesis of (±)-isoiridomyrmecin.

Recently, we have reported the novel Pd(0)-catalyzed cyclization of allylic acetates and allenic moieties.[1] The reaction is discriminated by the number of tether carbon chains as shown in eq 1. As we previously reported, the reaction (n = 2, path b) forms a new π-allylpalladium intermediate which underwent tandem cyclization *via* alkene insertion and carbonylation forming a tetracyclic diketone in one operation. On the other hand, the reaction (n = 3, path a) holds salient features as follows: (i) the novel regioselectivity in carbopalladation of allenes generating an alkenylpalladium intermediate,[2-4] (ii) cis selectivity in intraannular diastereoselection of the cyclization,[5] and (iii) subsequent carbonylation[6] giving an α-cyclopentylacrylic acid derivative. In application of the latter example, we considered the prospect of synthesizing iridoid monoterpenes. Herein we wish to report the synthesis of isoiridomyrmecin ((±)-**1**)[7] by way of the Pd(0)-catalyzed cyclization of 2-methyl-1-vinyl-5,6-heptadienyl acetate (**3**). Cyclization of **3** can provide the key intermediate **2a** which has correct stereochemistry and proper substituents for the syntheses of not only isoiridomyrmecin (**1**) but also dolichodial[8] and teucrium lactone.[9]

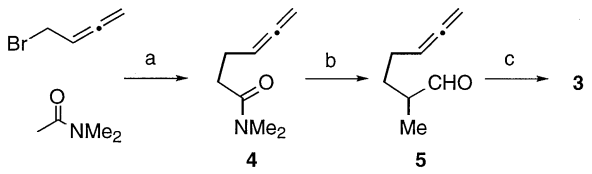


Scheme 1.



The substrate **3** was prepared as shown in Scheme 2. Alkylation of *N*,*N*-dimethylacetamide with 4-bromo-1,2-butadiene gave amide **4** in 86% yield. Addition of methyllithium to the amide **4**, followed by the Wittig reaction ($MeOCH{=}PPh_3$) of the resulting ketone gave aldehyde **5** after acid hydrolysis. Addition of vinyl magnesium bromide to the aldehyde **5**, followed by acetylation of the resulting allylic alcohol afforded the allylic acetates **3** as a diastereomer mixture in a ratio of 1.3 : 1. The overall yield of **3** was 40% in 5 steps from **4**.

Scheme 2.



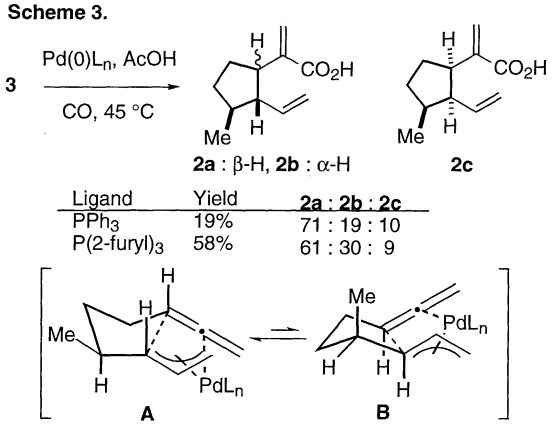
(a) LDA, HMPA, THF, -78 °C, 86%. (b) (i) MeLi, THF, -78 °C; (ii) $MeOCH_2PPh_3Cl$, BuLi, THF, -78 to 0 °C; (iii) 1 M HCl, THF, rt. (c) (i) $CH_2{=}CHMgBr$, THF, 0 °C; (ii) Ac_2O, pyridine, CH_2Cl_2, rt, 40% from **4**.

We examined the crucial Pd(0)-catalyzed cyclization-carbonylation using the diastereomer mixture of **3** because rapid epimerization of the terminal π-allylpalladium can lose the allylic stereogenic center prior to the cyclization.[10] Treatment of **3** with 10 mol% of tetrakistriphenylphosphinepalladium in acetic acid under a carbon monoxide atmosphere (1 atm) at 45 °C provided the products **2a**, **2b**, and **2c** in 19% yield in a ratio of 71 : 19 : 10. Although the yield was low,[11] the major product **2a** has the desired stereochemistry determined by NOE analysis.[12] The yield was improved by using $Pd_2(dba)_3{\bullet}CHCl_3$ (5 mol%) and P(2-furyl)$_3$ (30 mol%) as a catalyst up to 58% in this cyclization-carbonylation with slight decrease in stereoselectivity (61: 30: 9). The transition state **B** may be destabilized by an increase in the steric bulk of a methyl group at a pseudo axial position. Therefore, the reaction proceeds preferentially through transition state **A** having a pseudo equatorial methyl group leading to **2a**.

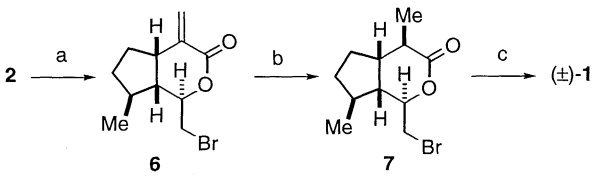
Bromolactonization of the diastereomer mixture of **2** afforded the corresponding lactones, which were easily separated by silica gel column chromatography. Alternatively, the desired diastereomer **6** was isolated in 82% yield based on **2a**. Hydrogenation of **6** for 2 d gave a mixture of diastereomers, **7** and α-epimer, in a ratio of 2.9 : 1. However, epimerization of the products was observed during the reaction and an equilibrium ratio of 5 : 1 was reached after 8 d. Reductive olefination of bromide **7** and successive treatment with ozone, sodium borohydride, and aqueous HCl gave the (±)-isoiridomyrmecin (**1**) in 57% overall yield.[13,14] The ^1H and ^{13}C NMR spectral data of synthetic **1** were identical with those of the reported isoiridomyrmecin.

It is demonstrated that the Pd(0)-catalyzed cyclization of **3**

Scheme 3.



Scheme 4.



(a) NBS, THF, 0 °C; chromatography, 82% based on **2a**. (b) H_2, Pd/C, MeOH, rt. (c) (i) Zn, EtOH, 78 °C; (ii) O_3, CH_2Cl_2/MeOH, -78 °C; $NaBH_4$, 0 °C; 3 M HCl, rt, 57% from **6**.

generated the 5-membered ring with two newly formed stereogenic centers as well as the acrylic acid moiety. This reaction can be used for other syntheses of iridoid monoterpenes. Further studies are underway in our laboratory.

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References and Notes

1 T. Doi, A. Yanagisawa, S. Nakanishi, K. Yamamoto, and T. Takahashi, *J. Org. Chem.*, **61**, 2602 (1996).

2 For *intermolecular* carbopalladation of allenes generating π-allylpalladium intermediates, see: a) R. R. Stevens and G. Shier, *J. Organomet. Chem.*, **21**, 495 (1970); b) I. Shimizu and J. Tsuji, *Chem. Lett.*, **1984**, 233; c) R. C. Larock, S. Varaprath, H. H. Lau, and C. A. Fellows, *J. Am. Chem. Soc.*, **106**, 5274 (1984); d) M. Ahmar, J.-J. Barieux, B. Cazes, and J. Gore, *Tetrahedron*, **43**, 513 (1987); e) Y. Yamamoto, M. Al-Masum, and N. Asao, *J. Am. Chem. Soc.*, **116**, 6019 (1994); f) B. M. Trost and V. J. Gerusz, *J. Am. Chem. Soc.*, **117**, 5156 (1995); g) R. Grigg, V. Sridharan, and C. Terrier, *Tetrahedron Lett.*, **37**, 4221 (1996).

3 For *intramolecular* version, see: S. Ma and E. Negishi, *J. Org. Chem.*, **59**, 4730 (1994); S. Ma and E. Negishi, *J. Am. Chem. Soc.*, **117**, 6345 (1995).

4 For amino- and alkoxy-palladation of allenes forming σ-vinylpalladium intermediates, see: H. Alper, F. W. Hartstock, and B. Despeyroux, *J. Chem. Soc., Chem. Commun.*, **1984**, 905; L. S. Hegedus, N. Kambe, R. Tamaru, and P. D. Woodgate, *Organometallics*, **2**, 1658 (1983); D. Lathbury, P. Vernon, and T. Gallagher, *Tetrahedron Lett.*, **27**, 6009 (1986); D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy, and T. Gallagher, *J. Am. Chem. Soc.*, **113**, 2652 (1991); M. Kimura, K. Fugami, S. Tanaka, and Y. Tamaru, *J. Org. Chem.*, **57**, 6377 (1992).

5 The trans selectivity is dominant in the cyclization of 2,7-octadienyl acetates, see: M. Terakado, K. Murai, M. Miyazawa, and K. Yamamoto, *Tetrahedron*, **50**, 5705 (1994).

6 A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, **39**, 3318 (1974); A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, **33**, 2379 (1994).

7 For isolation, see: G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Aust. J. Chem.*, **9**, 288 (1956). For related stereocontrolled syntheses of iridomyrmecin or isoiridomyrmecin, see: K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959); M. M. Abelman, R. L. Funk, and J. D. Munger, Jr., *J. Am. Chem. Soc.*, **104**, 4030 (1982); W. Oppolzer and E. J. Jacobsen, *Tetrahedron Lett.*, **27**, 1141 (1986); K. Mikami, K. Takahashi, and T. Nakai, *Synlett*, **1989**, 45; J. D. Kilburn, *Tetrahedron Lett.*, **31**, 2193 (1990); J. M. Takacs and Y. C. Myoung, *Tetrahedron Lett.*, **33**, 317 (1992); Y. Yokoyama and K. Tsuchikura, *Tetrahedron Lett.*, **33**, 2823 (1992).

8 G. W. K. Cavil and H. Hinterberger, *Aust. J. Chem.*, **13**, 514 (1960); **14**, 143 (1961).

9 U. M. Pagnoni, A. Pinetti, R. Trave, and L. Garanti, *Aust. J. Chem.*, **29**, 1375 (1976).

10 P. Corradini, G. Maglio, A. Musco, and G. Paiaro, *Chem. Commun.*, **1966**, 618; J. W. Faller, M. E. Thomsen, and M. J. Mattina, *J. Am. Chem. Soc.*, **93**, 2642 (1971); B. Bosnich and P. B. Mackenzie, *Pure & Appl. Chem.*, **54**, 189 (1982).

11 Presumably, the low yield is due to dimerization of the allenic moiety by a Pd(0) complex: G. D. Shier, *J. Organometal. Chem.*, **10**, P15 (1967); D. R. Coulson, *J. Org. Chem.*, **38**, 1483 (1973).

12 **2a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (d, J = 6.6 Hz, 3H), 1.2-1.4 (m, 1H), 1.6-1.7 (m, 1H), 1.7-1.9 (m, 2H), 1.9-2.0 (m, 1H), 2.39 (ddd, J = 9.2, 9.2, 6.6 Hz, 1H), 3.20 (ddd, J = 9.2, 9.2, 6.6 Hz, 1H), 4.8-4.9 (m, 2H), 5.46 (ddd, J = 17.8, 9.6, 9.2 Hz, 1H), 5.58 (s, 1H), 6.33 (s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.4, 141.7, 139.8, 125.6, 114.7, 54.0, 43.9, 40.3, 33.9, 29.7, 19.9; IR (neat) 3110, 2948, 1692, 1621, 1424, 1274, 1163, 946, 911, 736, 666 cm^{-1}.

13 P. Callant, R. Ongena, and M. Vandewalle, *Tetrahedron*, **37**, 2085 (1981).

14 The synthetic (±)-**1**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.2-1.4 (m, 2H), 1.6-1.7 (m, 1H), 1.8-2.2 (m, 4H), 2.31 (dq, J = 10.3, 6.6 Hz, 1H), 3.95 (t, J = 11.2 Hz, 1H), 4.35 (dd, J = 11.2, 6.3 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.5, 69.5, 45.3, 43.2, 39.1, 38.3, 35.8, 33.2, 19.2, 14.0; IR (neat) 2948, 2864, 1743, 1453, 1378, 1351, 1244, 1168, 1129, 1107, 1053, 1036, 1013, 721 cm^{-1}.