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ORGANOPALLADIUM APPROACHES TO PROSTAGLANDINS. 2.[1] SYNTHESIS OF PROSTAGLANDIN ENDOPEROXIDE ANALOGS VIA π-ALLYLPALLADIUM ADDITIONS TO BICYCLIC OLEFINS

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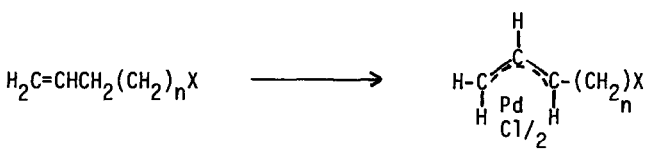
Summary: A variety of prostaglandin endoperoxide analogs are readily available by addition of π-allylpalladium compounds to bicyclic olefins and subsequent treatment with alkenyl and alkynyl organometallics. Pronounced biological activity is evident in these compounds.

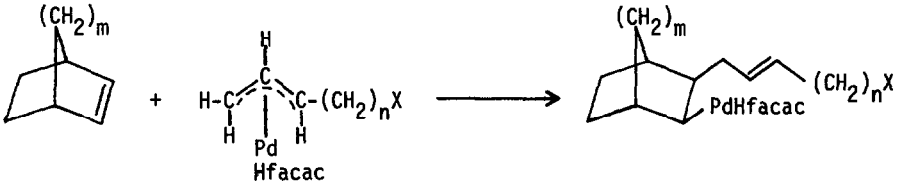
Since the discovery of the highly biologically active prostaglandin endoperoxides, great interest has been shown in the synthesis of analogs which might be more chemically and physiologically stable.[2] The majority of compounds synthesized so far have been prepared by Diels-Alder approaches or simple modification of the primary prostaglandins, and differ primarily in substitution of the peroxide linkage by more stable moieties. We wish to report a totally different approach to prostaglandin endoperoxide analogs, one which takes advantage of the ease with which π-allylpalladium compounds add to bicyclic olefins to generate stable, isolable alkylpalladium intermediates readily elaborated into prostaglandin endoperoxide analogs.

The requisite π-allylpalladium compounds are available now via several procedures directly from olefins. However, at the time this work was initiated, no good procedure was available for the direct conversion of terminal monosubstituted olefins to π-allylpalladium compounds, so we developed our own allylic chlorination-palladation sequence.[3] More recently, Trost has reported a more convenient procedure using $Pd(O_2CCF_3)_2$ which we have adopted.[4] Using Trost's procedure, except for methyl crotonate in which palladium chloride can be used,[5] we have prepared each of the following π-allylpalladium compounds.



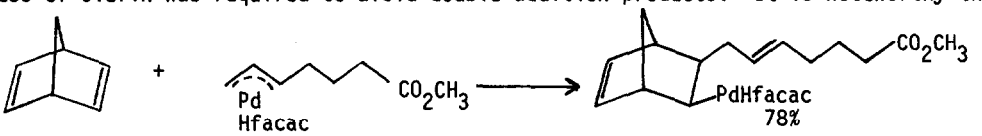
n	X	% Yield
0	CO_2CH_3	50
3	CO_2CH_3	81
7	CO_2CH_3	67
3	$CH_2OSiMe_2(t\text{-}Bu)$	46

Although these π-allylpalladium chlorides will not add directly to bicyclic olefins, anion exchange using AgOAc followed by hexafluoroacetylacetone affords the corresponding π-allylpalladium hexafluoroacetylacetonates which add readily to bicyclic olefins (1 equivalent, 24-48 hours at room temperature).[6] As indicated, additions to norbornene go very

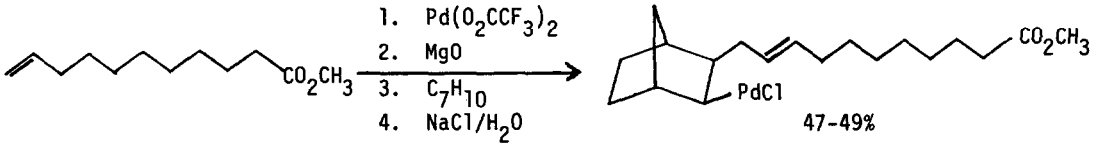


m	n	X	% Yield
1	0	CO_2CH_3	70-80
1	3	CO_2CH_3	90
1	3	$CH_2OSiMe_2(\underline{t}\text{-Bu})$	77
1	7	CO_2CH_3	78
2	3	CO_2CH_3	∿40

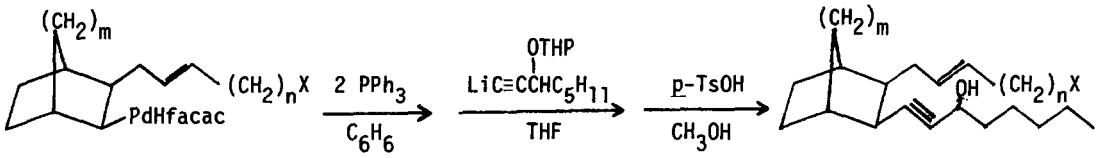
well, while bicyclo[2.2.2]octene gives lower yields. Norbornadiene also reacts readily, but an excess of olefin was required to avoid double addition products. It is noteworthy that



all of these olefins give exclusively the cis, exo adducts bearing a trans double bond in the side chain, since the addition of aryl-[1,7] and vinylpalladium[8] compounds to norbornadiene gives cis, endo addition. Several variations in this general procedure can be employed with equally good results. One can add AgOAc, then the olefin and finally the hexafluoroacetylacetone, and isolate comparable yields of the hexafluoroacetylacetonate adducts. Alternatively, one can prepare the π-allylpalladium trifluoroacetate according to Trost's procedure[4] and add this directly to the bicyclic olefin.



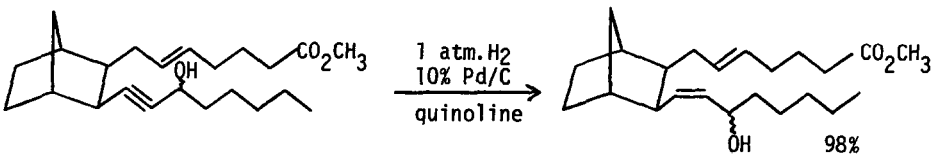
The unsaturated alcohol side chain is readily introduced using 2 equivalents of triphenylphosphine and 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne as discussed in our previous communication.[1] In this reaction, better results are obtained using the hexafluoroacetylacetonates than the chlorides. As indicated, deprotection affords prostaglandin endoperoxide



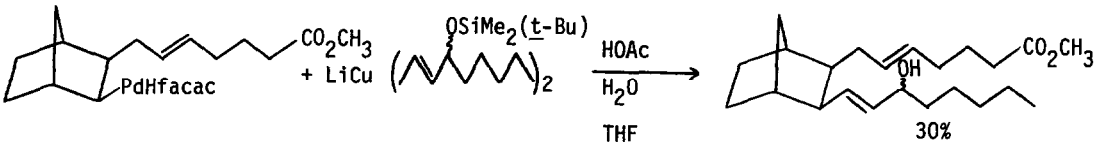
m	n	X	% yield THP	% yield alcohol
1	0	CO_2CH_3	57	90
1	3	CO_2CH_3	76	96
1	3	$CH_2OSiMe_2(t\text{-Bu})$	57	68 (diol)
1	7	CO_2CH_3	65	83
2	3	CO_2CH_3	53	82
norbornadiene adduct	3	CO_2CH_3	48	89

analogs in high yield and no difficulty is experienced with the ester functional group. Substitution proceeds with complete retention of the original exo-palladium stereochemistry. Saponification (2 N KOH, CH_3OH, 30 minutes at reflux) proceeds readily to give the corresponding carboxylic acids.

Both cis and trans allylic alcohols of this basic skeleton can also be prepared. Cis hydrogenation of the triple bond can be effected in high yield. The trans allylic alcohol

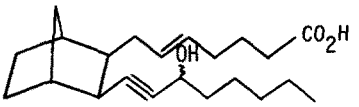


is most easily prepared by using vinylcopper reagents directly on the organopalladium intermediates. However, at present the yields are low and this reaction needs further



work. It is noteworthy that the α- and β- alcohols of this latter compound are readily separated by column chromatography.

Preliminary biological testing has been carried out on most of the compounds indicated above. All compounds exhibit some inhibition of blood platelet aggregation. The following compound, however, is extremely active, showing inhibition of blood platelet aggregation



approximately half that of PGE_1 and one-tenth that of prostacyclin, without any attempt yet having been made to separate the diastereomers or to prepare this compound in optically active form. Preliminary results indicate that this compound is a specific inhibitor of thromboxane synthetase. Complete biological results will be published elsewhere at a later date.

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References

1. For "Organopalladium Approaches to Prostaglandins. 1." see Tetrahedron Lett., in press.
2. (a) K. C. Nicolaou, G. P. Gasic and W. E. Barnette, Angew. Chem., Int. Ed. Eng., 17, 293 (1978); (b) K. C. Nicolaou and J. B. Smith in "Annual Reports in Medicinal Chemistry", Vol. 14, Chpt. 17, Academic Press, New York (1979); (c) T. J. Leeney, P. R. Marsham, G.A.F. Ritchie and M. W. Senior, Prostaglandins, 11, 953 (1976); (d) E. J. Corey, M. Shibasaki, K. C. Nicolaou, C. L. Malmsten and B. Samuelsson, Tetrahedron Lett., 737 (1976); (e) H. Shimomura, A. Sugie, J. Katsube and H. Yamamota, Tetrahedron Lett., 4099 (1976); (f) G. L. Bundy, Tetrahedron Lett., 1957 (1975); (g) P. S. Portoghese, D. L. Larson, A. G. Abatjoglou, E. W. Dunham, J. M. Gerrard and J. G. White, J. Med. Chem., 20 (1977); (h) G. L. Bundy and D. C. Peterson, Tetrahedron Lett., 41 (1978); (i) R. R. Gorman, G. L. Bundy, D. C. Peterson, F. F. Sun, O. V. Miller and F. A. Fitzpatrick, Proc. Nat. Acad. Sci. USA, 74, 4007 (1977); (j) E. J. Corey, K. Narasaka and M. Shibasaki, J. Am. Chem. Soc., 98, 6417 (1976); (k) E. J. Corey, B. Samuelsson, K. C. Nicolaou, Y. Machida and C. L. Malmsten, Proc. Nat. Acad. Sci. USA, 72, 3355 (1975); (l) H. Miyake, S. Iguchi, H. Itoh and M. Hayashi, J. Am. Chem. Soc., 99, 3536 (1977); (m) P. Wlodawer, B. Samuelsson, S. M. Albonico and E. J. Corey, J. Am. Chem. Soc., 93, 2815 (1971); (n) S. Ranganathan, D. Ranganathan and M. M. Mehrota, Tetrahedron Lett., 1851 (1978); (o) P. Barraclough, Tetrahedron Lett., 1897 (1980); (p) N. Hamanaka, S. Ohuchida, S. Hashimoto, S. Kosuge, S. Okuyama and M. Hayashi, Tennen Yuki Kagobutsu Toronkai Koen Yoshishu, 22nd, 649 (1979); (q) R. L. Jones and N. H. Wilson, Eur. Pat. Appl. 13,607 (1980); (r) P. W. Spraque, J. E. Heikes, D. N. Harris and R. Greenberg, Adv. Prostaglandin Thromboxane Res., 6, 493 (1980); (s) K. Sakai, K. Inoue, S. Amemiya, A. Morita and K. Kojima, Chem. Pharm. Bull., 28, 1814 (1980).
3. R. C. Larock and J. P. Burkhart, Syn. Commun., 9, 659 (1979).
4. B. M. Trost and P. J. Metzner, J. Am. Chem. Soc., 102, 3572 (1980).
5. J. Tsuji and S. Imamura, Bull. Chem. Soc. Japan, 40, 197 (1967).
6. (a) R. P. Hughes and J. Powell, J. Organometal. Chem., 30, C45 (1971); (b) M. C. Gallazzi, T. L. Hanlon, G. Vitulli and L. Porri, J. Organometal. Chem., 33, C45 (1971); (c) M. Zocchi, G. Tieghi and A. Albinati, J. Organometal. Chem., 33, C47 (1971); (d) M. Zocchi, G. Tieghi and A. Albinati, J. Chem. Soc., Dalton Trans., 883 (1973); (e) R. P. Hughes and J. Powell, J. Organometal. Chem., 60, 387, 427 (1973); (f) F. Dahan, Acta Cryst. B, 1941 (1976); (g) M. Zocchi and G. Tieghi, J. Chem. Soc., Dalton Trans., 944 (1979).
7. (a) A. Segnitz, P. M. Bailey and P. M. Maitlis, J. Chem. Soc., Chem. Commun., 698 (1973); (b) A. Segnitz, E. Kelly, S. H. Taylor and P. M. Maitlis, J. Organometal. Chem., 124, 113 (1977).
8. (a) E. Vedejs and P. D. Weeks, Tetrahedron Lett., 3207 (1974); (b) R. C. Larock, S. S. Hershberger, K. Takagi and M. A. Mitchell, Tetrahedron Lett., in press.

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