A Novel Transition Metal-Catalyzed Route to Functionalized Dihydropyrans and Tetrahydrooxepines

Floris P. J. T. Rutjes,* T. Martijn Kooistra, Henk Hiemstra and Hans E. Schoemaker[a]

Laboratory of Organic Chemistry, Amsterdam Institute of Molecular Studies, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

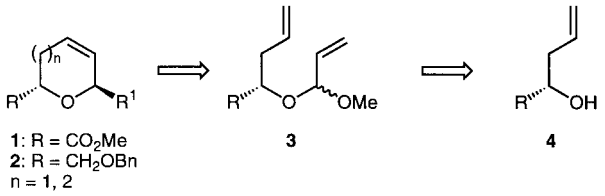
Fax +31 20 525 5670; e-mail: florisr@org.chem.uva.nl

[a]DSM Research, P.O. Box 18, 6160 MD Geleen, The Netherlands

Received 3 November 1997

Abstract: A straightforward route for the synthesis of α,α'-disubstituted dihydropyrans and tetrahydrooxepines has been developed involving Pd- and Ru-catalyzed reactions.

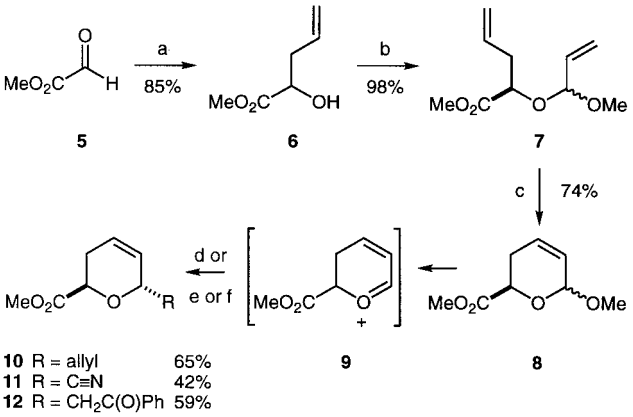
2,6-Disubstituted dihydropyrans **1** and **2** (n = 1) occur frequently in nature as a structural unit in a wide range of natural products.[1] In addition, these compounds could serve as useful building blocks for the synthesis of biologically active saturated oxygen heterocycles *via* functionalization of the double bond. Examples include (poly)cyclic ethers,[2] but also modified carbohydrates and 2-carboxyl-substituted tetrahydropyrans with antibacterial activity such as KDO.[3] More specifically, dihydropyrans **2** (R^1 = OMe) have recently been used as intermediates in the synthesis of mevinolin and compactin.[4,5] In conjunction with previous work in our group on vinylsilane-terminated formation of dihydropyrans *via* oxycarbenium ions,[6] we set out to explore a novel entry into this compound class, which would enable us to vary the side chains and would also give facile access to enantiopure heterocycles. Moreover, the methodology outlined in this paper is not restricted to six-membered ring formation, but can also be applied to form the corresponding seven-membered rings. Especially the latter aspect provides a significant benefit compared to previously established methods for forming such rings *via* hetero Diels-Alder reactions.[5,7] A short retrosynthetic outline of our route is shown in Scheme 1.



Scheme 1

The target compounds **1** and **2** should be accessible *via* the allylic acetal **3**, which contains (i) a terminal olefin function that can be used as a handle for ring-closing metathesis[8,9] and (ii) an acetal function to enable later modification of the system *via* oxycarbenium ion chemistry.

The first sequence (Scheme 2) commenced with anhydrous methyl glyoxylate (**5**),[10] which upon treatment with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane led to methyl 2-hydroxy-4-pentenoate (**6**). Initially, attempts were made to convert **6** into the desired allylic acetal under acid-catalyzed conditions with acrolein derivatives, but without much success. Therefore, we turned our attention to other strategies, involving the use of 1-methoxy-1,2-propadiene,[11] which upon electrophilic activation and subsequent reaction with the secondary alcohol might give rise to the desired product. Several methods have been published describing activation of allenes towards coupling with oxygen nucleophiles (including *N*-bromosuccinimide, $HgCl_2$),[11] but these routes are not attractive in view of the stoichiometric use of the reagents. At this point, a publication of Alper and coworkers appeared,[12] who obtained a similar acetal as a byproduct in Pd(II)-catalyzed annulation reactions with substituted allenes. Application of their conditions and

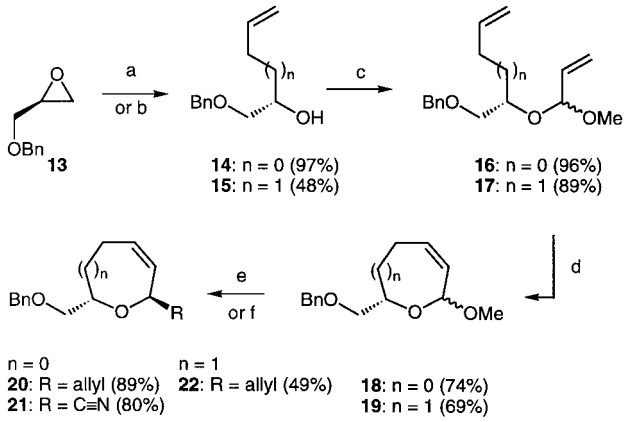


Reagents and conditions: (a) allyltrimethylsilane (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2 equiv.), CH_2Cl_2, 0 °C → rt; (b) $Pd(OAc)_2$ (5 mol%), dppp (5 mol%), 1-methoxy-1,2-propadiene (5.0 equiv.), Et_3N (1.5 equiv.), MeCN, reflux, 3 h; (c) $Cl_2(PCy_3)_2RuCHPh$ (5 mol%), CH_2Cl_2, rt, 4 h; (d) allyltrimethylsilane (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), CH_2Cl_2, 0 °C → rt; (e) trimethylsilyl cyanide (2.0 equiv), $BF_3{\cdot}OEt_2$ (2.0 equiv.), CH_2Cl_2, 0 °C → rt; (f) 1-phenyl-1-(trimethylsilyloxy)ethylene (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), CH_2Cl_2, 0 °C → rt.

Scheme 2

further optimization ($Pd(OAc)_2$ (cat.), $Ph_2P(CH_2)_3PPh_2$ (dppp), excess of 1-methoxy-1,2-propadiene, Et_3N, MeCN, 80 °C in a sealed tube) led to a virtually quantitative yield of the desired acetal **7**.[13] Not surprisingly, **7** was obtained as a *ca.* 1:1 mixture of diastereoisomers, which could not be separated by column chromatography. The diolefin **7** then cyclized smoothly under standard ring-closing metathesis conditions (5 mol% of Ru-benzylidene catalyst, 0.1 M solution in CH_2Cl_2, rt), providing the dihydropyran **8** in a satisfactory yield of 74% (*cis*/*trans* 1:1). This mixture of isomers was then treated with a Lewis acid ($BF_3{\cdot}OEt_2$) to generate the allylic oxycarbenium intermediate **9**, which in the presence of different nucleophiles (allyltrimethylsilane, trimethylsilyl cyanide and α-(trimethylsilyloxy)styrene reacted to the corresponding 1,2-adducts **10–12** in reasonable to good yields and excellent *trans*-selectivity. This selectivity probably arises from stereoelectronically preferred *pseudo*-axial attack of the incoming nucleophile[14] and is more generally found in similar unsaturated systems.[15,16]

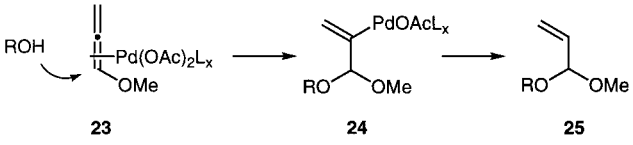
An analogous sequence was developed to arrive at enantiopure six- and seven-membered ring ethers as depicted in Scheme 3. Starting material was the readily available benzyl-protected (*R*)-glycidol **13**, which was ring-opened with complete regioselectivity using vinyl- or allylmagnesium bromide in the presence of Me_2S and a catalytic amount of CuI to give the corresponding secondary alcohols **14** and **15**, respectively. A similar strategy as in the previous scheme, namely oxypalladation of 1-methoxy-1,2-propadiene (in both cases *ca.* 1:1 mixture of isomers were formed) and subsequent ring-closing metathesis provided the oxygen heterocycles **18** and **19** (*cis*/*trans* 1:1) in



Reagents and conditions: (a) CH_2=CHMgBr (1.8 equiv.), CuI (20 mol%), Me_2S (1.6 equiv.), THF, 0 °C, 2 h; (b) CH_2=$CHCH_2$MgBr (1.8 equiv.), CuI (20 mol%), Me_2S (1.6 equiv.), THF, 0 °C, 2 h; (c) $Pd(OAc)_2$ (5 mol%), dppp (5 mol%), 1-methoxy-1,2-propadiene (5.0 equiv.), Et_3N (1.5 equiv.), MeCN, reflux, 3 h; (d) $Cl_2(PCy_3)_2$RuCHPh (5 mol%), CH_2Cl_2, rt, 4 h; (e) allyltrimethylsilane (2.0 equiv.), BF_3·OEt_2 (2.0 equiv.), CH_2Cl_2, 0 ° C → rt; (f) trimethylsilyl cyanide (2.0 equiv.), BF_3·OEt_2 (2.0 equiv), CH_2Cl_2, 0 °C → rt.

Scheme 3

satisfactory yields. In the six-membered ring series, the oxycarbenium ion-mediated coupling reactions with allyltrimethylsilane and trimethylsilyl cyanide proceeded considerably better than in the ester-substituted cases leading to the desired dihydropyrans **20** and **21** in good yields. Again, coupling took place selectively at the 2-position, with complete *trans*-selectivity.[15,16] Although the addition to the seven-membered ring oxycarbenium ion did not proceed in high yield, a single diastereoisomer (**22**) was obtained whose stereochemistry in analogy with the six-membered rings was tentatively assigned as *trans*.[16]



Scheme 4

The proposed mechanism of the Pd-catalyzed oxypalladation of methoxyallene is shown in Scheme 4, where coordination of the Pd(II)-species with the more electron-rich oxygen-substituted double bond (*viz*. **23**) renders the allene sufficiently electrophilic to be attacked by the secondary alcohol.[17] Protonolysis of the resulting vinyl-palladium species **24** then leads to the desired acetal **25** and regeneration of the Pd(II)-catalyst.

In conclusion, we have developed an efficient route to various 2,6-*trans*-disubstituted oxygen heterocycles, which can also be appplied to form the corresponding seven-membered rings. The pathway involves (i) a novel Pd(II)-mediated coupling of 1-methoxy-1,2-propadiene with secondary alcohols and (ii) a Ru-catalyzed ring-closing process as the key transformations. One could envision that the use of similar allylic acetals is not only restricted to ring-closing metathesis, but that they could also be applied in many other types of ring-closing processes. At present, we are exploring such possibilities including applications in natural product synthesis, which will be presented in the near future.

References

1) For some examples, see *e.g.*: (a) Norcross, R.D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041; (b) Faulkner, D.J. *Nat. Prod. Rep.* **1997**, *14*, 259.

2) (a) Gleason, M.M.; McDonald, F.E. *J. Org. Chem.* **1997**, *62*, 6432; (b) Rychnovsky, S.D.; Dahanukar, V.H. *J. Org. Chem.* **1996**, *61*, 7648.

3) (a) Gao, J.; Härter, R.; Gordon, D.M.; Whitesides, G.M. *J. Org. Chem.* **1994**, *59*, 3714; (b) Kragl, U.; Gödde, A.; Wandrey, C.; Lubin, N.; Augé, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 119.

4) (a) Bauer, T.; Chapuis, C.; Jezewski, A.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymm.* **1996**, *7*, 1391; (b) Bauer, T.; Jezewski, A.; Jurczak, J. *Tetrahedron: Asymm.* **1996**, *7*, 1405.

5) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935.

6) Semeyn, C.; Blaauw, R.H.; Hiemstra, H.; Speckamp, W.N. *J. Org. Chem.* **1997**, *62*, 3426.

7) For a review article, see: Bednarski, M.D.; Lyssikatos, J.P. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, 661 and references cited therein.

8) For reviews, see: (a) Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc. Chem. Res.* **1995**, *28*, 446; (b) Schmalz, H.-G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1833; (c) Mol, J.C.; Ivin K.J. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: London, 1997.

9) For a selection of recent examples, see: (a) Rutjes, F.P.J.T.; Schoemaker, H.E. *Tetrahedron Lett.* **1997**, *38*, 677; (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K.C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166; (c) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 5925; (d) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130 and references cited therein.

10) Hook, J.M. *Synth. Commun.* **1984**, *14*, 83.

11) For a review article about 1-alkoxy-1,2-propadienes, see: Zimmer, R. *Synthesis*, **1993**, 167.

12) Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566.

13) All new compounds were obtained in analytically pure form and appropriately characterized by IR, ^{1}H and ^{13}C NMR, high resolution mass data and rotational values.

14) For a discussion of the stereoelectronic aspects of the addition reaction, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209-221.

15) The *trans*-relationship was established by comparison of ^{1}H NMR NOE data (obtained *via* irradiation of the α-oxygen hydrogen atoms) with those of related structures (*e.g.* ref. 6). For related coupling reactions with cyclic allylic oxycarbenium ions selectively giving *trans*-disubstituted products, see: Postema, M.H.D. *Tetrahedron* **1992**, *48*, 8572-8576 and references cited therein.

16) Data for selected compounds:
11: colorless oil; R_f = 0.46 (silica, 70% ether in petroleum ether); IR (film) ν_{max} 2956, 2240, 1745, 1186, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10-6.15 (m, 1H), 5.74-5.79 (m, 1H), 5.18 (dd, *J* = 1.7, 3.5 Hz, 1H), 4.50 (dd, *J* = 5.5, 8.8 Hz, 1H), 3.81 (s, 3H), 2.42-2.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 127.7, 121.0, 116.1, 69.8, 62.6, 52.4, 26.7; HRMS (EI), calcd for $C_8H_9NO_3$ (M^+): 167.0582, found 167.0594.
21: colorless oil; R_f = 0.65 (silica, 70% ether in petroleum ether); $[\alpha]_D^{22}$ -57.4 (*c* 0.5, CH_2Cl_2); IR (film) ν_{max} 3031, 2868, 2234, 1104, 904, 739, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-

7.38 (m, 5H), 6.08-6.13 (m, 1H), 5.70-5.74 (m, 1H), 5.04-5.06 (m, 1H), 4.60 (s, 2H), 4.07-4.13 (m, 1H), 3.59 (d, *J* = 4.5 Hz, 1H), 2.26-2.34 (m, 1H), 2.01-2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 128.9, 128.3, 127.7, 127.6, 120.9, 116.9, 73.3, 71.5, 70.7, 62.9, 26.2; HRMS (EI), calcd for $C_{14}H_{15}NO_2$ (M^+): 229.1103, found 229.1107.

22: colorless oil; R_f = 0.74 (silica, 70% ether in petroleum ether); $[\alpha]_D^{22}$ -0.5 (*c* 1, CH_2Cl_2); IR (film) ν_{max} 3020, 2927, 2859, 1093, 743, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m, 5H), 5.83-5.93 (m, 1H), 5.70-5.76 (m, 1H), 5.49 (ddd, *J* = 1.8, 3.8, 11.1 Hz, 1H), 5.04-5.12 (m, 2H), 4.56 (s, 2H), 4.44-4.49 (m, 1H), 4.07 (dt, *J* = 5.1, 10.7 Hz, 1H), 3.57 (dd, *J* = 6.1, 9.9 Hz, 1H), 3.45 (dd, *J* = 5.0, 9.9 Hz, 1H), 2.21-2.40 (m, 4H), 1.81-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.3, 132.5, 130.7, 128.2, 127.5, 127.4, 116.6, 75.4, 73.2, 72.4, 71.0, 40.3, 29.9, 26.4; HRMS (FAB), calcd for $C_{17}H_{23}O_2$ ($M+H^+$): 259.1698, found 259.1682.

17) For an excellent summary of Pd-chemistry, see: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.