Pergamon

Tetrahedron Letters 39 (1998) 1905–1908

TETRAHEDRON LETTERS

Diastereospecific Synthesis of Spiro[4.5]decan-2-ones as Vetivane Precursor via Rhodium Catalysed Claisen Rearrangement / Hydroacylation

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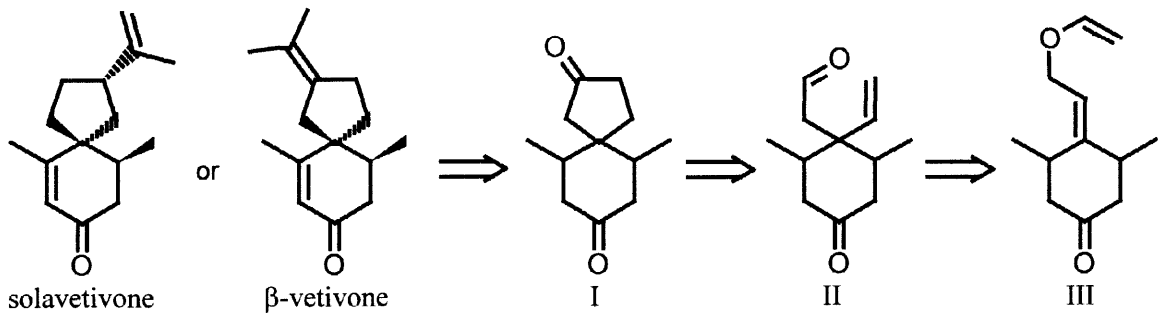
Received 15 December 1997; accepted 21 January 1998

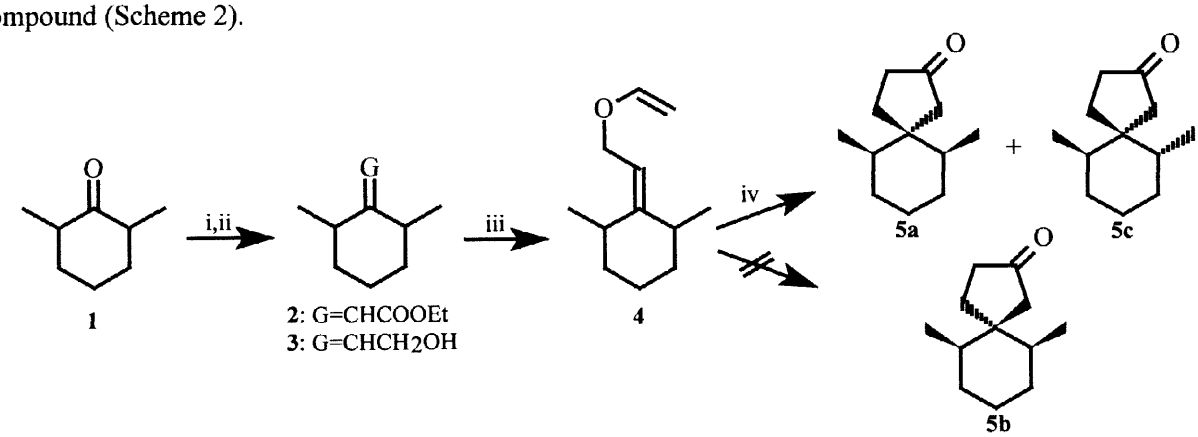
Abstract: The one-pot combination of Claisen rearrangement of allyl vinyl ethers followed by an intramolecular hydroacylation catalysed by RhCl(cod)(dppe) is used as a key step in the synthesis of *meso*-dimethyl-1,4-dioxa-dispiro[4.2.4.2]tetradecan-10-one (**12**). The diastereospecific outcome of the reaction is discussed. This product is a potential precursor in the synthesis of solavetivone.

Construction of the spirovetivane carbon-skeleton as found in solavetivone or β-vetivone requires diastereoselective construction of the spiro[4.5]decane framework and regiospecific formation of at least one double bond. Recently we demonstrated the application of a one-pot combination of Claisen rearrangement / hydroacylation[1] in the formal total synthesis of acoradienes[2]. In this paper we wish to report on the synthesis of a C_S-symmetrical precursor for solavetivone[3], a phytoalexin of the Solanaceae family[4]. A retrosynthetical analysis applying our method of spirocyclopentanellation[5] is outlined in Scheme 1.



Scheme 1

This route requires cyclisation of pentenal **II** via intramolecular hydroacylation. **II** is derived from allyl vinyl ether **III** which can be prepared from an appropiate substituted cyclohexandione. To achieve regioselective transformation at one of both keto-functionalities in **I** protection of the cyclohexanone moiety is necessary. We decided first to test the reaction sequence starting from 2,6-dimethylcylohexanone (**1**) as a model compound (Scheme 2).



Scheme 2 i: $(EtO)_2P(O)CH_2COOEt$, NaH, PhH, 33%; ii: DIBAH, Et_2O, 80%, iii: $EtOCH{=}CH_2$, 1.5mol% $Hg(OAc)_2$, 72%; iv: Δ, 5mol% RhCl(cod)(dppe), >95% GLC, 42% isol.;

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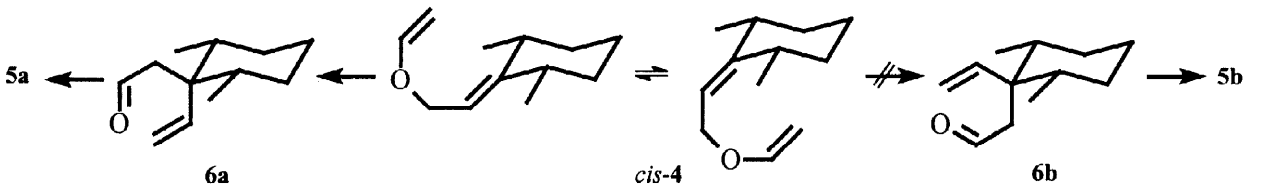
0040-4039/98/$19.00
PII: S0040-4039(98)00197-X

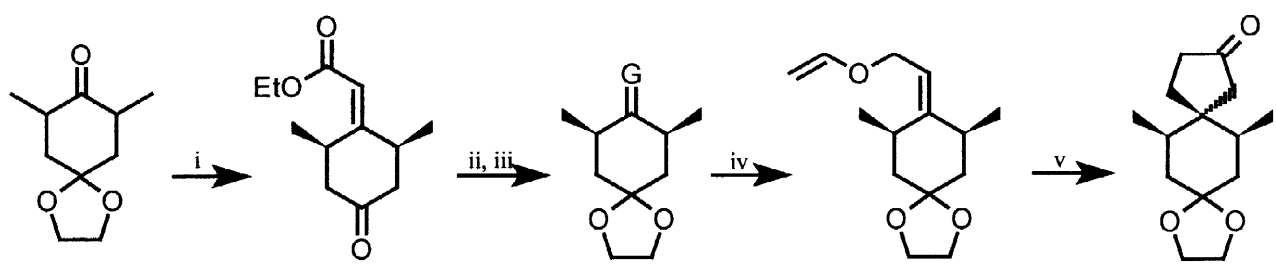
Ether **4** was obtained as a mixture of isomers in a *cis/trans* ratio of 2:1. Upon heating in benzonitrile as a solvent in the presence of 5mol% RhCl(cod)(dppe), ether **4** was converted to the corresponding spiroanellated cyclopentanones **5** in more than 95% yield as determined by GLC[6]. During workup and isolation of the pure material some loss has to be encountered due to the high boiling point of the solvent. Pure **5** is isolated in 42% yield as a mixture of diastereoisomers[7] **5a** and **5c** in a 4:3-ratio which are readily separated by MPLC. Noteworthy 6*t*,10*t*-dimethyl-(5*r*C[1])-spiro[4.5]decan-2-one[8] **5a** is the single of two possible products formed from ether **4** with *cis*-orientation of the methyl substituents. As shown in Scheme 3 the stereochemistry is determined during the Claisen rearrangement step of the one-pot procedure.



Scheme 3

The sigmatropic reaction of *cis*-**4** exclusively takes place under equatorial attack leading to 4-pentenal **6a** instead of **6b**. Facial selectivity is also observed by House[9a] and Gilbert[9b] for the rearrangement of comparable allyl vinyl ethers with an exocyclic double bond.

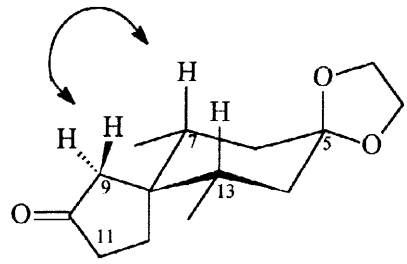
To introduce the proper functionality allowing further manipulation directed towards the biologically active spirovetivanes, a reaction sequence similar to that described above was carried out starting with 7,9-dimethyl-1,4-dioxa-spiro[4.5]decan-8-one (**7**)[10]. Since Wittig-Horner reaction gave unsatisfactory results, olefination was achieved by addition of *in situ* generated lithiumethoxyacetylide[11] to the carbonyl compound and acid-catalyzed rearrangement of the intermediate alcohol. Under these conditions deprotection and equilibration occur and *cis*-**8** is the sole product obtained, regardless of the *cis/trans*-ratio of the starting material **7**.



Scheme 4 i: LDA, $ClCH_2CH(OEt)_2$, H^+, 60%; ii: $CH_3(OCH_3)_3$, $HOCH_2CH_2OH$, 92%; iii: DIBAH, Et_2O, 68%; iv: $EtOCH{=}CH_2$, 1.5mol% $Hg(OAc)_2$, 63%; v: Δ, 10mol% RhCl(cod)(dppe), 35% GLC;

After reprotection of the remaining carbonyl function, ester **9** is reduced and the resulting allylic alcohol **10** transvinylated to yield ether **11**[12] using Watanabe's method[13]. The one-pot reaction sequence to convert **11** to spirocyclic pentanone **12**[14] does not proceed as smoothly as it does in the case of ether **4**. Besides cyclopentanone **12** several unidentified byproducts of lower molecular weight are formed. This very likely is due to the acidic character of the rhodium-species generated during the catalytic process affecting the ketal protection group, and we are currently investigating other catalytic systems to improve the tolerance towards acid-sensitive groups. However, 7*t*,13*t*-dimethyl-1,4-dioxa-(8*r*C[9])-dispiro[4.2.4.2]tetradecan-10-one (**12**) was isolated by preparative TLC. Relative stereochemistry was assigned by NOESY-NMR spectra. A well defined cross peak between the singlet of C9-H_2 and the methine protons at C7/C13 clearly establishes the

7*t*,13*t*-(8*r*C^9)-configuration as shown in Scheme 5. No cross peak was observed between the triplets of C11-H_2 or C12-H_2 and the methine signal of C7/C13.



7*t*,13*t*-(8*r*C^9)-**12**

Scheme 5

The relative stereochemistry of this *meso* product resembles that of solavetivone. Introduction of the internal double-bond can best be achieved by oxidation of the corresponding silyl-enol-ether with $Pd(OAc)_2$[15]. According to described procedures such silyl-enol-ethers can be prepared enantioselectively from *meso*-cyclohexanone moieties with the aid of chiral lithium amide bases[16], thereby introducing optical activity to the achiral *meso*-compound by means of desymmetrization[17].

ACKNOWLEDGEMENT: We wish to thank the Deutsche Forschungsgemeinschaft (DFG) for financial support and the DEGUSSA AG. Hanau, for the generous donation of rhodium(III)chloride.

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6. 0.90g (5mmol) 2-vinyloxy-ethylidene-(2,6-dimethylcyclohexane) (**4**) and 161mg (0.25mmol, 5mol%) RhCl(cod)(dppe) are heated in 3ml dry benzonitrile under an Ar atmosphere for 10h at 175°C. After cooling to room temperature the crude reaction mixture is chromatographed on silica gel (hexanes/methyl^{t}butyl-ether 10:1).
7. Both compounds were obtained by Marshall during his work on the elucidation of the structure of β-vetivone, J.A. Marshall, P.C. Johnson, *J. Org. Chem.* **1970**, *35*, 192-196. spectroscopic data 6*t*,10*t*-dimethyl-(5*r*C^1)-spiro[4.5]decan-2-one (**5a**): GC-MS (EI, 70eV): m/z (%)= 181 (M^++1, 28), 163 (44), 123 (46), 109 (92), 95 (63), 81 (100), 67 (95); IR (film, NaCl): $\tilde{\nu}$[cm^{-1}]= 2958, 2919, 2853, 1741, 1471, 1460, 1444, 1149; ^{1}H NMR (400MHz, $CDCl_3$): δ[ppm]= 2.27 (t*, *J*=8.7Hz, 2H, C3-H_2), 2.24 (s, 2H, C1-H_2), 1.74 (t*, *J*=8.7Hz, 2H, C4-H_2), 1.65 (m, 1H, C8-HH), 1.47 (m, 2H, C6-H, C10-H), 1.4-1.1 (m, 5H), 0.86 (d, *J*=6.6Hz, 6H, 2*CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ[ppm]= 221.3 C2, 48.6 C1, 45.8 C5, 41.7 C6/C10, 39.2 C3, 31.2 C7/C9, 26.1 C8, 19.7 C4, 16.9 2*CH_3; spectroscopic data 6*c*,10*t*-dimethyl-(5*r*C^1)-spiro[4.5]decan-2-one (**5c**): GC-MS (EI, 70eV): m/z (%)= 181 (M^++1, 28), 163 (73), 123 (37), 109 (100), 95 (39), 81 (75), 67 (51); IR (film, NaCl): $\tilde{\nu}$[cm^{-1}]= 2959, 2921, 2855, 1740, 1465, 1405, 1379; ^{1}H NMR

NMR (400MHz, $CDCl_3$): δ[ppm]= 2.30 (d, *J*=18.3Hz, 1H), 2.24 (brs, 2H), 2.01 (d, *J*=18.3Hz, 1H), 1.8-1.6 (m, 3H), 1.48 (m, 3H), 1.4-1.0 (4H), 0.89 (d, *J*=6.2 Hz, 3H), 0.87 (d, *J*=6.8Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ[ppm]= 221.0 C2, 48.2 CH_2, 45.7 Cq, 41.8 CH, 41.7 CH, 37.8 CH_2, 31.1 CH_2, 30.4 CH_2, 26.2 CH_2, 20.1 CH_2, 16.3 CH_3, 15.3 CH_3;

8. Relative stereochemistry is designated by *"c"* and *"t"* to denote a *cis* or *trans* relationship to some reference (*"r"*) substituent according to Beilstein, E III, Vol. VI, Part7, Springer Verlag, Berlin, **1967**, S. x. See also reference (7).
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12. Spectroscopic data 7,9-dimethyl-8-(2-vinyloxy-ethylidene)-1,4-dioxa-spiro[4.5]decane (**11**): GC-MS (EI, 70eV): m/z (%)= 238 (M^+, 2), 196 (100), 165 (2), 153 (5), 139 (11), 129 (12), 113 (62), 87 (20); IR (film, NaCl): $\tilde{\nu}$[cm^{-1}]= 3116, 2958, 2936, 2878, 1634, 1612, 1460, 1371, 1316, 1196; ^1H NMR (400 MHz, $CDCl_3$): δ[ppm]= 6.48 (ddd*, *J*= 14.3Hz, *J*=6.8Hz, *J*=1.0Hz, 1H), 5.35 (t*, *J*=6.2Hz, 1H), 4.42 (dd, *J*=6.8Hz, *J*=12.1Hz, 1H), 4.33 (dd, *J*=5.9Hz, *J*=12.1Hz, 1H); 4.18 (dt*, *J*=14.3Hz, *J*=1.8Hz, 1H), 4.01 (dt*, *J*=6.9Hz, *J*=1.8Hz, 1H), 3.94 (m, 4H), 2.74 (sext*, *J*=7.0Hz, 1H), 2.46 (mc, 1H), 1.83 (mc, 2H), 1.64 (dd, *J*=13.3Hz, *J*=7.5Hz, 1H), 1.52 (dd, *J*=9.5Hz, *J*=13.3Hz, 1H), 1.24 (d, *J*=7.3Hz, 3H), 1.14 (d, *J*=7.0Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ[ppm]= 151.4 CH, 148.8 Cq, 117.4 CH, 108.8 Cq, 86.6 CH_2, 64.4 CH_2, 64.3 CH_2, 63.6 CH_2, 42.6 CH_2, 41.8 CH_2, 36.1 CH, 33.0 CH, 21.3 CH_3, 20.5 CH_3;
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14. 240mg (1.0mmol) 7,9-dimethyl-8-(2-vinyloxy-ethylidene)-1,4-dioxa-spiro[4.5]decane (**11**) und 60mg (0.1mmol, 10mol%) RhCl(cod)(dppe) are heated in 1ml dry benzonitrile under an Ar atmosphere for 14h at 150°C. The crude product is filtered through a short column using neutral aluminia and Et_2O. The solvent is removed by Kugelrohr distillation (90°C, 20mbar). The portion of **12** in the residue (250mg) is 35% as established by GLC. A sample of **12** was isolated using preparative TLC (silica, hexanes/methyl^{t}butyl-ether 2:1). spectroscopic data 7*t*,13*t*-dimethyl-1,4-dioxa-(8*r*C^9)-dispiro[4.2.4.2]-tetradecan-10-one (**12**): MS (EI, 70eV): m/z (%)= 238 (M^+, 1), 210 (2), 194 (2), 181 (2), 149 (2), 134 (2), 113 (100), 86 (22), 49 (7), 55 (4); IR ($CDCl_3$): $\tilde{\nu}$[cm^{-1}]= 2961, 2927, 2884, 1732, 1472, 1381, 1261, 1159, 1085, 963; ^1H NMR (400MHz, $CDCl_3$): δ[ppm]= 3.95 (brs, 4H, C2-H_2+C3-H_2), 2.30 (t*, 2H, *J*=8.9Hz, C11-H_2), 2.27 (s, 2H, C9-H_2), 1.83 (m, 2H, C7-H+C13-H), 1.78 (t*, 2H, *J*=8.9Hz, C12-H_2), 1.62-1.44 (m, 4H, C6-H_2+C14-H_2), 0.90 (d, 6H, *J*=7.5Hz, 2*CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ [ppm]= 220.5 C10, 108.3 C5, 64.3/64.2 C2/C3, 47.8 C9, 45.0 C8, 39.8 C6+C14, 39.0 C11, 38.8 C7+C13, 18.7 C12, 16.6 2*CH_3;
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