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Intramolecular Horner-Wadsworth-Emmons Reaction in Base Sensitive Substrates: Enantiospecific Synthesis of Iridoid Monoterpene Lactones[#]

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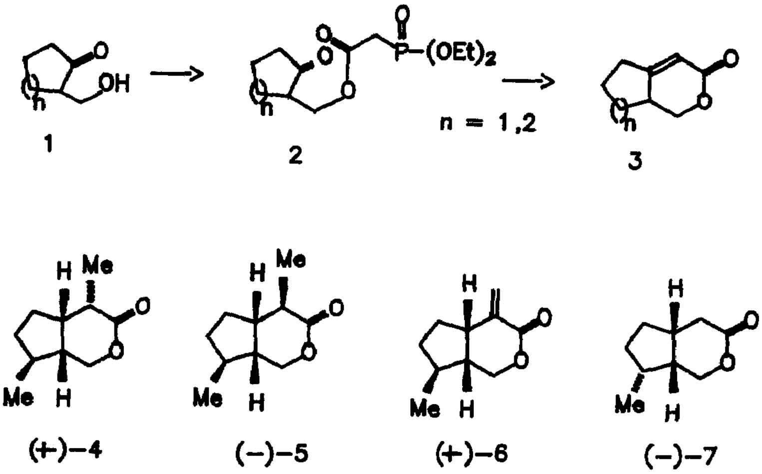
Abstract: The cyclopentapyranones (-)-7 and (-)-13, representing the <u>cis</u>-fused 9-carbon core of iridoid lactones, are synthesised from (+)-pulegone.

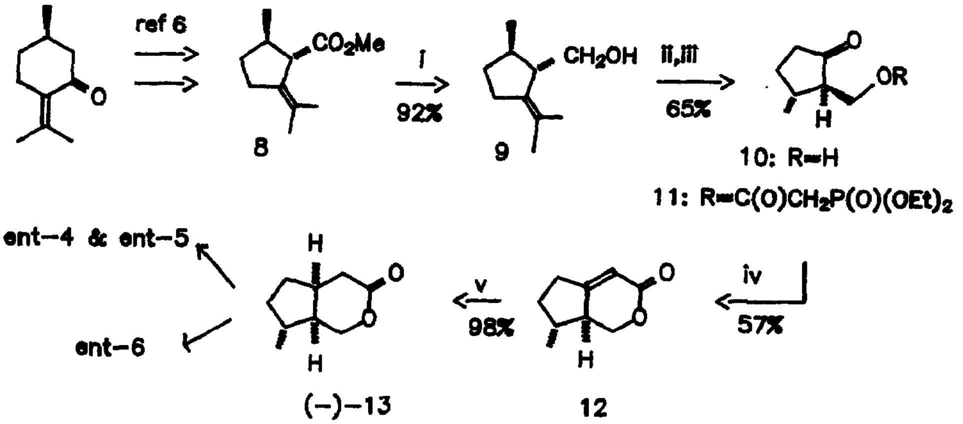
The Horner-Wadsworth-Emmons (HWE) reaction is an important C=C bond forming process in natural product synthesis.[1] A large number of base/solvent conditions are reported for performing the HWE reaction on base sensitive substrates which are prone to α-epimerisation and/or β-elimination.[2] Of the four possible combinations for the reaction of phosphonate anion with carbonyl compound (intra- vs inter-molecular; aldehyde vs ketone), the intramolecular variation with ketones is the most difficult. This is because (i) it is not possible to react the preformed phosphonate anion with ketone, (ii) the base is directly competing for all possible acidic sites on the substrate, and (iii) the C-C bond forming process is slower than in aldehydes. Micolajczyk and Midure[3] have used sulfur stabilised phosphonate anions to overcome the problem of β-elimination in the synthesis of unsaturated δ-lactones from hydroxy-carbonyl compounds. Some time ago we synthesised model cyclopentapyranone and cyclohexapyranone systems 3 from β-hydroxy ketones 1 using intramolecular HWE (IMHWE) conditions that avoided formation of exocyclic enones[4] (Scheme 1). However, the issue of possible α-epimerisation could not be addressed in compounds 2,3.

The iridoid lactones iridomyrmecin (4), isoiridomyrmecin (5), teucriumlactone (6) and boschnialactone (7) have attracted the attention of synthetic organic chemists for over three decades now.[5] They are logical synthetic targets owing to their interesting biological activity and the presence of three contiguous non-epimerisable stereogenic centres on the bicyclic backbone. We report in this Letter the IMHWE reaction on 2-hydroxymethyl cyclopentanones derived from R-pulegone leading to iridoid metabolites 4-7 without concomitant β-elimination and α-epimerisation.

SCHEME-1

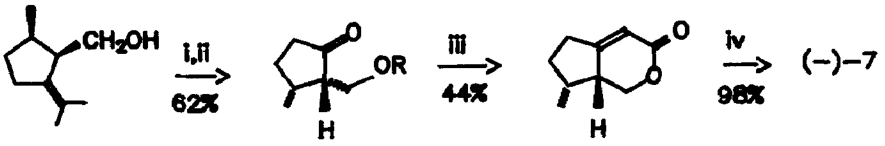


SCHEME-2



Reagents (i) LAH, ether, 0°C (ii) O_3, $NaHCO_3$, CH_2Cl_2, -78°C; then DMS, 0°C (iii) $(EtO)_2P(O)CH_2CO_2H$, DCC, CH_2Cl_2 (iv) DBU, LiCl, CH_3CN, rt, 1h (v) 5% Pd/C, H_2, EtOAc, 4h

SCHEME-3



14 15: $R=C(O)CH_2P(O)(OEt)_2$ 16

Reagents (i) O_3, $NaHCO_3$, CH_2Cl_2, -78°C; then DMS, 0°C (ii) $(EtO)_2P(O)CH_2CO_2H$, DCC, CH_2Cl_2 (iii) DIPEA, LiCl, CH_3CN, rt, 16h (iv) 5% Pd/C, H_2, EtOAc, 4h

trans-Methyl pulegenate[6] (8) was reduced (LAH) and ozonised under buffered conditions (-78°C, $NaHCO_3$, DMS work-up) to provide the somewhat unstable β-hydroxy ketone 10. Esterification of alcohol 10 with diethylphosphonoacetic acid under neutral conditions (DCC) provided phosphonate 11. Exposure of substrate 11 to IMHWE conditions (DBU, LiCl, 1h) cleanly provided the unsaturated lactone 12 in 57% yield after column chromatography (Scheme 2). Highly stereoselective *exo*-face hydrogenation (H_2, Pd/C) occurred to install the third stereogenic centre and afforded pyranone (-)-13[5,†] in excellent ee. Since the *cis*-fused pyranone 13 is the penultimate precursor in the synthesis of iridoid lactones 4-6, a formal synthesis of *ent*-(-)-(4), *ent*-(+)-(5) and *ent*-(-)-(6) is accomplished.

Inspection of boschnialactone (7)[7] reveals that it will arise from *cis*-homoallylic alcohol 14. LAH reduction of a 60:40 mixture of *cis*- and *trans*-ethyl pulegenates[6] followed by silica gel purification afforded the *cis*-alcohol 14, which was uneventfuly converted to keto phosphonate 15 (Scheme 3). Subjecting phosphonate 15 to IMHWE conditions (DBU, LiCl, 1h) afforded lactone 16 along with minor amounts of epimeric 12. However, use of milder conditions (DIPEA = $(i\text{-}Pr)_2NEt$, LiCl, 16h) resulted in exclusive formation of desired lactone 16 as evidenced from ^1H NMR analysis at 200 MHz. It is noteworthy that the less stable and easily epimerisable *cis* stereochemistry was completely retained under the mild yet facile reaction conditions. Again, highly stereoselective *exo*-face hydrogenation completed the synthesis of (-)-(7).[7,†]

The use of conventional bases[1,2] such as NaH, NaOMe, t-BuOK, K_2CO_3, Cs_2CO_3, $LiOH.H_2O$, etc. resulted in partial or complete elimination. The IMHWE reaction is successfully employed on base sensitive ketones to synthesise iridoid natural products in a highly enantio- and diastereocontrolled manner from R-pulegone. The easy availability of S-pulegone[8] from S-citronellol makes the sequence adaptable to the synthesis of natural metabolites 4-6. Structurally related natural products[9] such as dihydronepetalactone, mitsugashiwalactone and onikulactone are currently being targeted.

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References and Notes:

\# *Dedicated to Prof. S. Ranganathan on his 60th birthday.*

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† All new compounds gave satisfactory spectroscopic and analytical data. Optical rotation for (-)-(13): $[\alpha]^{25}_{D}$: -92.0 (c 1.0 in $CHCl_3$), -82.0 (c 0.5 in CCl_4); Reported $[\alpha]^{25}_{D}$: -72.49 (c 1.67 in CCl_4).

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