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STEREOCONTROLLED SYNTHESIS OF (±)-RECIFEIOLIDE VIA ORGANOPALLADIUM CHEMISTRY

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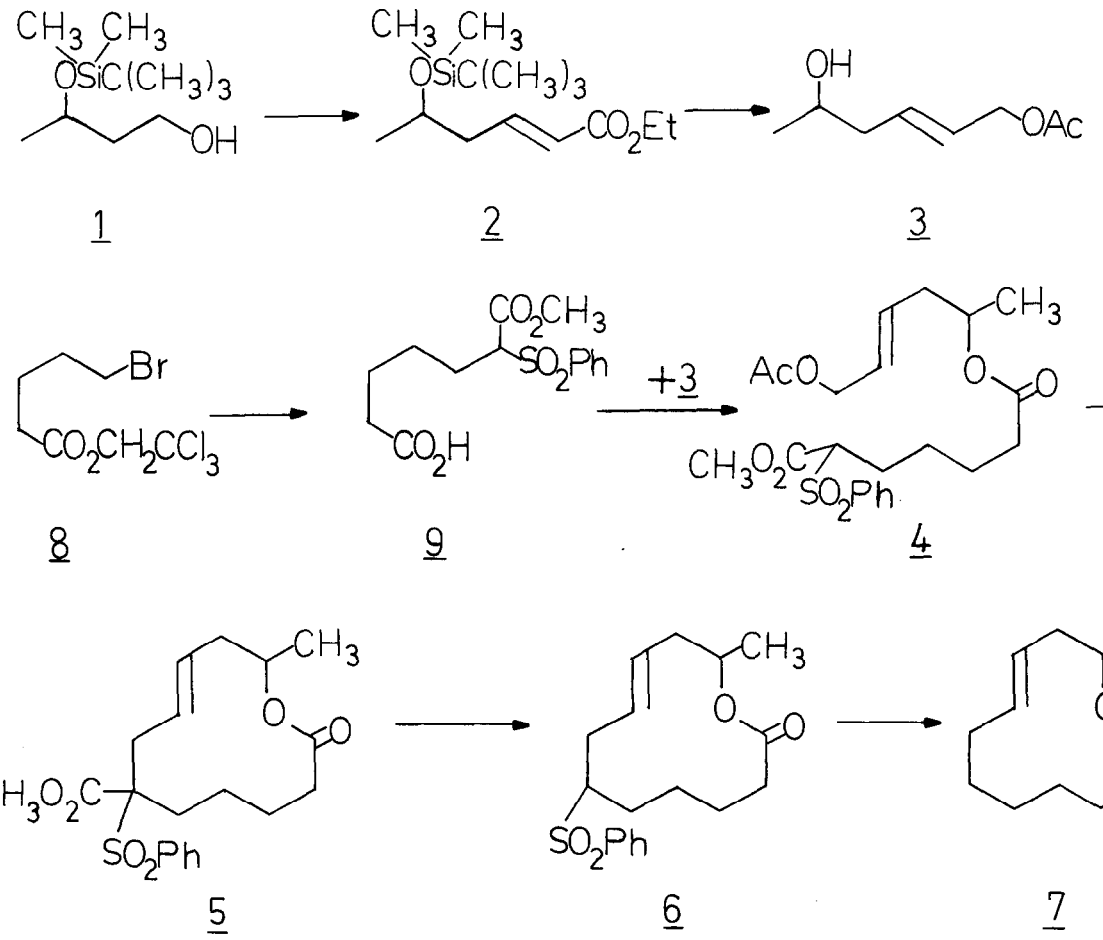
While impressive strides have been made in macrolide synthesis via macrolactonization routes[1], a general method for preparation of macrolides via C-C bond fusion has to date been lacking[1,2]. The preparation of lactones via C-C bond formation rather than the more conventional lactonization routes potentially provides a greater degree of flexibility in devising synthetic strategies directed toward the growing number of naturally occurring macrolides[3]. In particular, one may employ a convergent synthetic scheme, allowing synthesis of alcohol and acid portions independently which can then be readily condensed, forming the ester linkage prior to ring closure. A general macrolactonization method recently developed and utilized by ourselves[4] and others[5] involves the use of organopalladium chemistry. We now wish to report the application of this methodology in the total synthesis of (±)-recifeiolide[6], a naturally occurring macrolide isolated[7] from the fungus Cephalosporium recifei.

The alcohol portion 3 was readily synthesized starting from tert-butyldimethylsilyl ether 1. Oxidation with pyridinium chlorochromate (2 equiv., NaOAc, CH_2Cl_2, R.T.), followed by an Emmons-Wadsworth-Horner condensation ($(EtO)_2POCH_2CO_2Et$, NaH, THF, -78°-0°C) afforded the E-α,β unsaturated ester 2. Reduction with diisobutylaluminum hydride (toluene, 0°C) followed by acylation (AcCl, pyridine, CH_2Cl_2, 0°C) and hydrolysis of the silyl ether ($HClO_4$, THF-H_2O, R.T.) afforded 3[8] in an overall 53% yield from 1. Acid portion 9 was available in two steps from the β,β,β-trichloroethyl ester of 5-bromo-pentanoic acid, 8. Alkylation of the sodium salt of methyl phenylsulfonylacetate (DMSO, 50°C) and reductive hydrolysis (Zn, DMF, 0°C)[9] gave acid 9 in 84% yield. Conversion of 9 to its acid chloride ($SOCl_2$) and condensation with alcohol 3 (Et_2O, pyridine 0°-40°C) gave the requisite precursor 4[8] in 79% yield. Conversion of 4 to the anion with NaH in THF and addition of the resultant solution via a syringe pump to a refluxing solution of 9 mole % $Pd(Ph_3P)_4$ produced only the 12-membered lactone 5[8] (m.p. 126-129.5°C) in 78% yield. Examination of the NMR spectrum at 270MHz revealed the presence of a trans double bond (J = 15.5 Hz), and absence of any terminal vinyl group which would have resulted from reaction at the allylically related carbon. In addition to the first example of 12 membered ring formation, the complete regio-

(no ten membered ring) and stereospecificity (no Z isomer) of this cyclization is quite noteworthy--especially compared to the intermolecular version[10]. Completion of the synthesis was accomplished by decarbomethoxylation to 6 ($(CH_3)_4\overset{+-}{N}OAc$, HMPA, 95°C) (86%) followed by reductive desulfonylation (6% Na-Hg, Na_2HPO_4, EtOH-THF, -25°C)[11] (94%) to give (±)-recifeiolide, 7[8], identical by spectroscopic (ir, nmr, ms) and chromatographic (tlc, vpc) criteria to an authentic sample[12].

The high regio- and stereospecificity of this cyclization approach thus provides a viable alternative for the formation of medium and large ring lactones. In addition, the sulfone-ester moiety present in the initially cyclized product may also serve to introduce further functionalization in the molecule. The consequences of this are actively being pursued in our laboratories.



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8. 3: ^{1}H-NMR ($CDCl_3$): δ 5.79 (d of t, J = 15.4, 6.9 Hz, 1H), 5.65 (d of t, J = 15.4, 6.1 Hz, 1H), 4.53 (d, J = 6.1 Hz, 2H), 3.85 (m, 1H), 2.72 (b, 1H), 2.23 (bt, J = 6.6 Hz, 2H), 2.07 (s, 3H), 1.19 (d, J = 6.1 Hz, 3H).
   4: ^{1}H-NMR ($CDCl_3$): δ 7.87 (bd, J = 7 Hz, 2H), 7.70 (bt, J = 7 Hz, 1H), 7.57 (t, J = 7 Hz,

2H), 5.65 (m, 2H), 4.92 (m, 1H), 4.50 (d, J = 5 Hz, 2H), 3.96 (d of d, J = 10.5, 5 Hz, 1H), 3.65 (s, 3H), 2.28 (m, 4H), 2.05 (s, 3H), 1.98 (m, 2H), 1.61 (m, 2H), 1.35 (m, 2H), 1.18 (d, J = 6 Hz, 3H).

5: ^{1}H-NMR ($CDCl_3$): δ 7.79 (bt, J = 6.8 Hz, 2H), 7.67 (m, 1H), 7.56 (m, 2H), 5.88 (d of d of t, J = 15.5, 11, 2 Hz, 0.4H), 5.56 (d of d of d of d, J = 15.3, 11, 3.5, 2 Hz, 0.6H), 5.37 (d of d of d of d, J = 15.5, 10.5, 4, 2 Hz, 0.4H), 5.20 (m, 1H), 5.13 (d of d of t, J = 15.3, 11, 2 Hz, 0.6 H), 3.62 (s, 3H), 3.03 (m, 1H), 2.80 (d of d, J = 13.6, 11.0 Hz, 0.6H), 2.55 (d of d, J = 16.5, 11.5 Hz, 0.4H), 2.47-2.14 (m, 5H), 1.43 (m, 2H), 1.27 (d, J = 6.4 Hz, 0.4H), 1.23 (d, J = 6.4 Hz, 0.6H).

7: ^{13}C-NMR ($CDCl_3$): δ 173.2, 133.4, 127.1, 68.5, 41.1, 33.0, 30.4, 25.1, 24.8, 24.3, 23.4, 20.6.

All nmr spectra were recorded at 270 MHz. All new compounds have been fully characterized including determination of elemental composition.

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12. We are grateful to Prof. H. Gerlach, Laboratorium für Organishe Chemie der Eidgenössischen Technischen Hochschule, Zurich, for the reference sample and to Prof. E. J. Corey, Harvard University, Cambridge, Mass., for spectral data.