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AN INTRAMOLECULAR DIELS-ALDER APPROACH TO THE SYNTHESIS OF THE RIGHT HAND HALF OF THE IONOPHORE ANTIBIOTIC X-14547A

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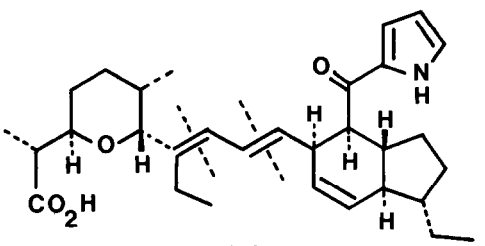
ABSTRACT: Starting from ethylbutyrate, an efficient synthesis of the right hand half of the antibiotic X-14547A has been achieved in which the desired five relative chiral centres were created by an intramolecular Diels-Alder reaction.

The recently isolated novel ionophore X-14547A (1) has been shown to possess interesting biological properties[1]. Although its total synthesis has not yet been achieved, it is the subject of considerable current effort.

Here we report our progress towards the construction of a suitably functionalised right hand portion of this important molecule.

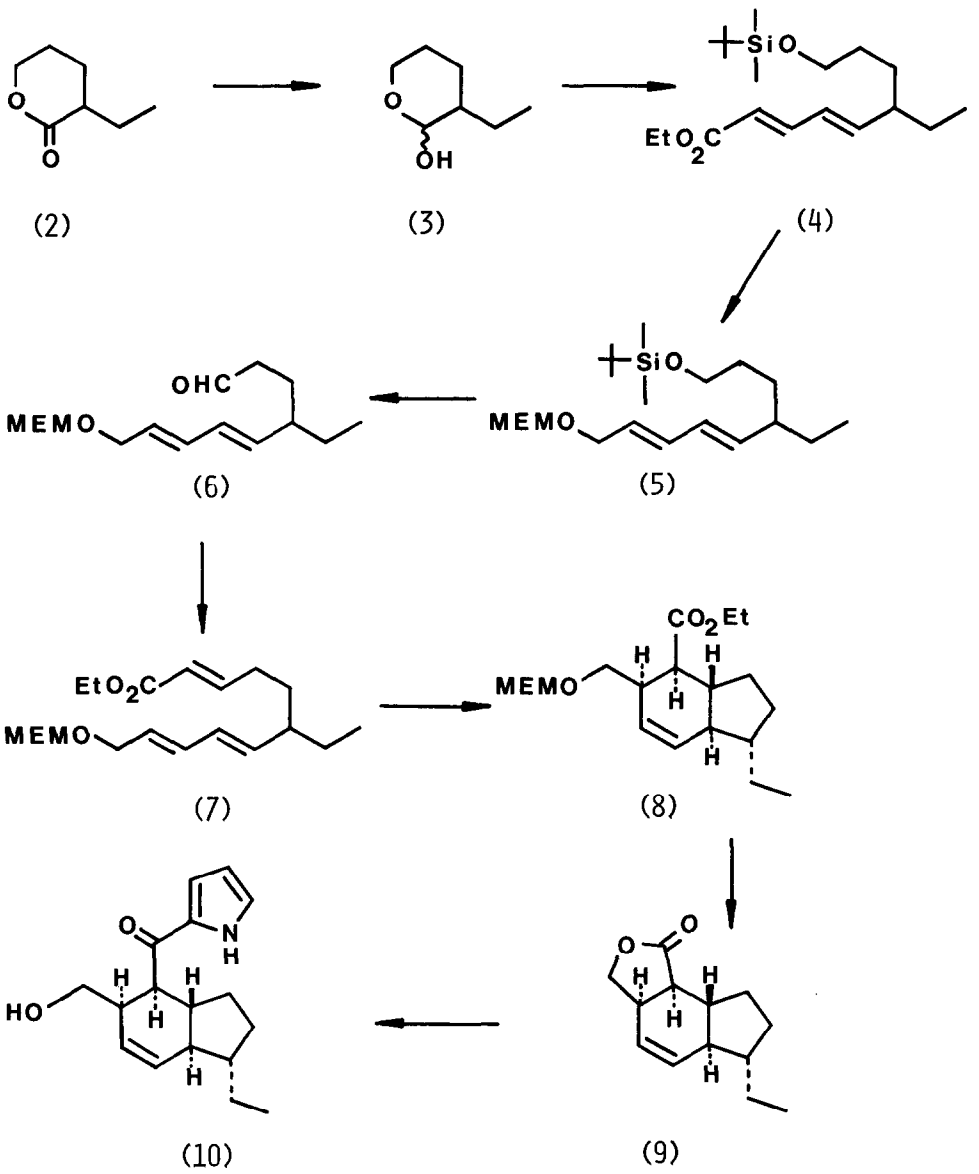


(1)

A retrosynthetic analysis suggests that (1) might be constructed by coupling between two appropriately protected fragments derived from either of the two disconnections in (1) above. The tetrahydroindan fragment is most logically derived by an intramolecular Diels-Alder approach[2,3] as discussed in this letter.

2-Ethyl-δ-valerolactone (2) was conveniently prepared from ethylbutyrate by alkylation of the enolate with 1-trimethylsilyloxy-3-iodopropane followed by hydrolytic work up and cyclisation in warm toluene/P.T.S.A. Direct alkylation of δ-valerolactone was less satisfactory in our hands, particularly on a large scale.

The lactone (2) was converted, in quantitative yield, to a mixture of lactols (3)[4] by treatment with DIBAL in toluene at -78°C. While (4) could be prepared in low yield, by Wittig reaction of the surprisingly unreactive lactols (3) with 3-(ethoxycarbonylallylidene)triphenyl-



phosphorane followed by protection, it was best obtained by silylation of (3) with t-butyldimethylsilyl chloride/imidazole and subsequent reaction with ethyl-4-diethylphosphonocrotonate/L.D.A. to give (4) in 72% overall yield. The E,E-dienoate (4) was smoothly reduced with 2.2 equiv. of DIBAL in toluene at $0^{o}C$ to the corresponding alcohol which was protected as its MEM ether (5) by reaction with MEM-chloride and diisopropylethylamine in CH_2Cl_2 in 96% overall yield from (4). Removal of the t-butyldimethylsilyl group with 2.5 equiv. of

tetra-n-butylammonium fluoride in T.H.F followed by oxidation of the resulting alcohol with CrO_3/pyridine in CH_2Cl_2 gave the aldehyde (6), again in 96% overall yield.

Reaction of (6) with carboethoxymethylenetriphenylphosphorane in CH_2Cl_2 at 25°C cleanly gave the E,E,E-trienoate (7) in 95% yield after removal of triphenylphosphine oxide.

With (7) now readily available, its intramolecular Diels-Alder cyclisation was investigated. Molecular models indicated that, of the two possible cis-endo cyclisation modes[5], the one involving the sterically least hindered transition state would provide the required five relative chiral centres of the desired tetrahydroindan moiety. On heating (7) in argon-flushed toluene at reflux for 36-70 h, the cyclised product (8) was obtained as a chromatographically homogeneous compound in near quantitative yield. A detailed high field (250 MHz) ^1H n.m.r. examination of this product showed that only small amounts (<10%) of the other possible isomers were present. Removal of the MEM protecting group with freshly fused $ZnBr_2$ in CH_2Cl_2 led to spontaneous lactonisation to the crystalline tricyclic lactone (9), m.p. 67.5-68.5°C in 60% overall yield from (7).

Contrary to the results of Bean[6] on the acylation of pyrryl Grignards, the ester (8) was remarkably unreactive to pyrryl magnesium bromide even under forcing conditions but reaction of the lactone (9) with pyrryl magnesium bromide in toluene[7] at 100-105° gave the desired hydroxypyrrolecarbonyl compound (10) in 73% yield.

We are currently investigating synthetic routes to the left hand portion of X-14547A together with refinements to the above synthesis.

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2. For recent reviews of intramolecular Diels-Alder reactions see W. Oppolzer, Angew. Chem Internat. Edn., 1977, 16, 10 and G. Brieger and J.N. Bennett, Chem. Rev., 1980, 80, 63.
3. Professors K.C. Nicolaou and W.R. Roush have each independently employed an intramolecular Diels-Alder reaction approach to the synthesis of the tetrahydroindan portion of X-14547A; we thank them for their kind exchange of information prior to publication. Prof. Nicolaou has also confirmed the structural assignment of the same lactone (9) by X-ray crystallography.
4. All new compounds were fully characterised by spectroscopic methods, acc. mass and/or microanalysis. ^1H n.m.r. data (250 MHz), δ/ppm ($CDCl_3$):
Compound (8): 5.95 (1H, d, J 10.26 Hz), 5.55 (1H, ddd, J 10.26, 4, 2.56 Hz), 4.63 (1H, d, J 6.7 Hz), 4.59 (1H, d, J 6.7 Hz), 4.1 (2H, dq, J 6.7, 1.53 Hz), 3.67 (2H, m), 3.5 (2H, m),

3.47 (2H, m), 3.39 (3H, s), 2.88 (1H, m), 2.62 (1H, dd, J 11.2, 6.7 Hz), 2.05-1.1 (9H, m), 1.28 (3H, t, J 6.7 Hz), and 0.91 (3H, t, J 7.2 Hz).

Compound (9): 6.07 (1H, d, J 10.2 Hz), 5.58 (1H, ddd, J 10.2, 3.82, 2.03 Hz), 4.51 (1H, q of dd, J 17.17, 4.5, 1.4 Hz), 4.51 (1H, m), 3.9 (1H, m), 3.2 (1H, m), 1.99 (2H, m), 1.8-1.1 (7H, m) and 0.95 (3H, t, J 7.14 Hz).

Compound (10): 10.03 (1H, brs, D_2O exch.), 7.1 (1H, m), 6.9 (1H, m), 6.3 (1H, m), 6.1 (1H, d, J 10.1 Hz), 5.6 (1H, dt, J 10.1, 3.2 Hz), 3.65 (2H, m), 3.46 (1H, dd, J 10.5, 7.01 Hz), 2.94 (1H, brs, D_2O exch.), 2.74 (1H, m), 2.2-1.0 (9H, m), and 0.92 (3H, t, J 7.35 Hz).

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