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REACTION OF LITHIUM DIMETHYLCUPRATE WITH CONFORMATIONALLY BIASED β-ACYLOXY ENOL ESTERS — REGIO AND STEREOCONTROLLED ACCESS TO FUNCTIONALIZED SIX-CARBON CHIRAL SYNTHONS[1]

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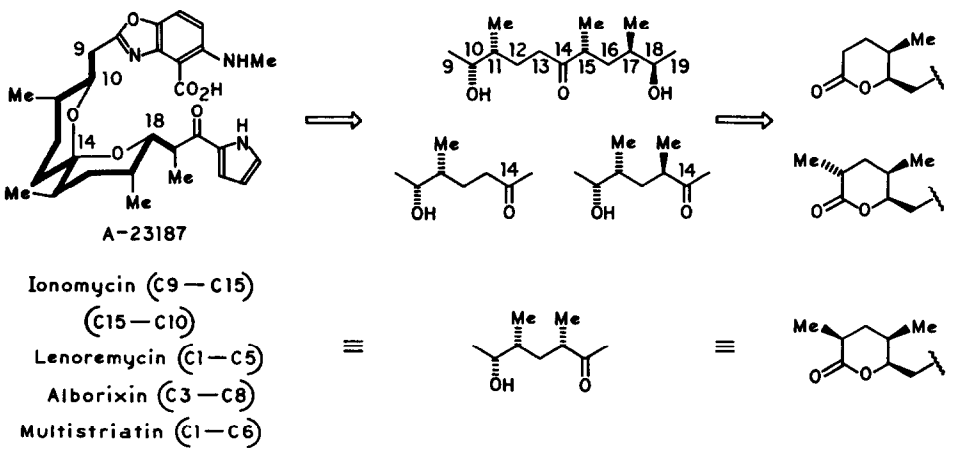
Summary: *Alkyl 2-acyloxy α-D-erythro-hex-2-enopyranoside diesters, readily available from D-hexoses, are versatile intermediates for the expeditious preparation of six-carbon chiral synthons containing alternating and/or consecutive C-methyl and hydroxyl groups.*

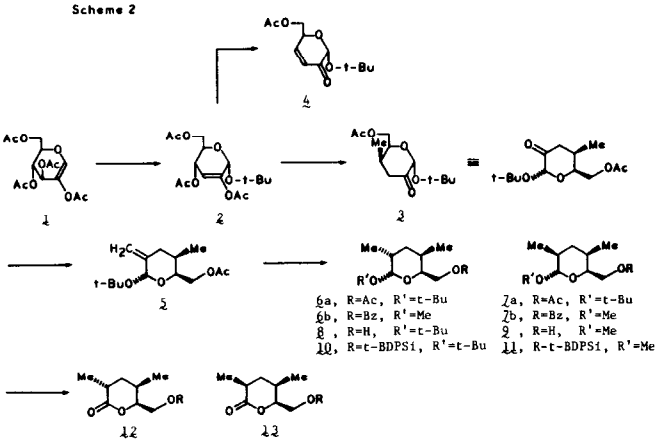
Recent efforts toward the total synthesis of natural products that are biosynthetically derived from the so-called "propionate" pathway[3] have necessitated the development of synthetic routes leading to carbon chains with multiple centers of chirality. In spite of several innovative approaches realized through elaboration of acyclic[4] or cyclic[5] precursors, achieving high levels of individual diastereomeric purity continues to be a major challenge. An alternate, operationally different strategy which addresses itself to this fundamental problem is based on the concept of "chiral templates"[6] derived from carbohydrates. This strategy has been useful in creating four consecutive chiral centers in six-carbon chains[7]. Other natural products contain as part of their carbon framework, consecutive *as well as* alternating C-methyl and hydroxyl substituents representing branching patterns that are somewhat less readily accessible by direct C-C bond forming reactions, not to mention the very demanding stereochemical requirements associated with such targets (Scheme 1). We describe herein a synthetically expedient solution to this problem.

Scheme 1



Tri-O-acetyl-2-acetoxy-D-glucal 1[8], is a crystalline substance, readily available from D-glucose in three high-yielding steps. Treatment of 1 with t-butanol and BF_3 etherate according to Ferrier[9] gave the new crystalline t-butyl α-D-glycoside 2[10] in 84% yield, mp 63-63.5°; $[\alpha]_D$ + 84.3° (Scheme 2). Treatment of 2 with lithium dimethylcuprate (2 equiv. in THF, 0°, 30 min) gave *in one step*, the corresponding 4-C-methyl derivative 3 in 60% yield, as a syrup, $[\alpha]_D$+ 141.4°. Alternatively, treatment of the enoside 2 with the anion of dimethyl methylphosphonate (3 equiv; in THF, -25°, then 25°, 1h) followed by cooling to -20° and adding the cuprate reagent (1 equiv; 0°, 30 min) gave the same derivative 3 in 70% yield. Enone 4, undoubtedly an intermediate in these reactions could also be prepared in 78% yield $[\alpha]_D$+ 2.8°, by treatment of 2 with 2.5 equiv. of dimethyl methylphosphonate anion (0°, 3h). Addition of the cuprate reagent to the enone 4 afforded a 83% yield of the expected 3. Introduction of a C-methyl group at C-2 was done via a Wittig reaction using methylenetriphenylphosphorane (85°, toluene, 30 min) to give the desired 5 in 84% yield, $[\alpha]_D$+ 163°. Hydrogenation in the presence of Wilkinson's catalyst ($(Ph_3P)_3$ RhCl H_2, benzene) followed by chromatographic separation, gave a 1:1 mixture of the 2(R), 4(R) isomer 6a, $[\alpha]_D$+ 112° and the 2(S), 4(R) isomer 7a, $[\alpha]_D$+ 81.1°, in over 95% yield. The corresponding neopentyl glycoside gave similar results indicating that in spite of the bulk of the anomeric substituent the axial orientation of the C-4 methyl group had a profound influence on the stereochemistry of the reduction, which, under normal circumstances should favor the 2(R), 4(R) isomer.[11,12] Quite surprisingly, catalytic hydrogenation of 5 in the presence of 10% Pd/C led to a 7:3 mixture in favor of the 2(S), 4(R) isomer. The methyl glycoside analog of 2 in the benzoate series is a readily available, crystalline substance.[9] It underwent essentially the same reactions shown in Scheme 2, except that catalytic hydrogenation (10%, Pd/C, H_2, toluene), gave the 2(S), 4(R) isomer 7b (76%); $[\alpha]_D$+ 83.3° and the 2(R), 4(R) isomer 6b (15%); $[\alpha]_D$+ 93%. Deacetylation of 6a and 7a gave 8 $[\alpha]_D$+ 125.5° and 9, $[\alpha]_D$+ 76.7°, respectively. Since acid hydrolysis of these substances led in part to 1,6-anhydro derivatives rather than the expected lactols, they were initially converted into the

Scheme 2



a t-BuOH, BF_3, b Me_2CuLi, c $(MeO)_2\overset{O}{P}CH_2Li$, d $Ph_3P{=}CH_2$, e $(Ph_3P)_3RhCl$,H_2
f aq AcOH, THF, g Collins

corresponding t-butyldiphenylsilyl ethers[13] 10 $[\alpha]_D$+ 47.8° and 11 $[\alpha]_D$+ 44.4°, and subsequently hydrolyzed (aq. AcOH, THF, 25°) and oxidised (Collins, 25°) to give the lactones 12, mp 123-124°C $[\alpha]_D$+ 17.3°; and 13, $[\alpha]_D$+ 37.6° (85%, 2 steps). N.m.r. studies on the lactones indicated that no epimerization had taken place during their preparation.

The transformation 2 → 3 is a novel reaction of an organocuprate with a β-acyloxy enol ester and may be a general C-C bond forming process applicable to related systems in acyclic derivatives as well.[14] The mechanism most probably involves initial attack of the cuprate on the enol ester function, generating an enone such as 4, which undergoes 1,4-conjugate addition as usual. The stereospecific formation of the 4(R) isomers in the acetate and benzoate series can be attributed to a more favored axial attack on a conformationally biased substrate.[15] The formation of the enone 4 from the treatment of 3 with a carbanion further reflects on the particular reactivity of β-acyloxy enol esters toward nucleophiles in general[16] and offers an expedient route to this class of synthetically useful compounds previously prepared by more elaborate processes.

The readily available enolones[17] are also susceptible to conjugate addition. Thus, treatment of the enolone 14[17] with lithium dimethylcuprate (THF, 0°, 2h) gave a crystalline product (88%), mp 136°; $[\alpha]_D$+ 73.7°, whose spectral and chemical properties are in agreement with the enone structure 15[18] (Scheme 3).

Scheme 3

14 15

In summary, the readily available and crystalline enosides such as 2 are versatile immediate precursors to enones such as 4, as well as to regio- and stereospecifically functionalized six-carbon compounds having contiguous R (methyl) and R (hydroxyl) groups with erythro stereochemistry. These can be transformed in two further steps into synthons containing a set each of *alternating* C-methyl groups and *consecutive* C-methyl and hydroxyl groups. Thus, intermediates such as 6a and 3 (after deoxygenation at C-2), are each suitably protected synthetic precursors of appropriate segments of the 1,7-dioxaspiro [5:5] undecance skeleton in the ionophore antibiotic A-23187[19,20] (Scheme 1). Compounds 7a and 9 readily obtained from the corresponding enosides, harbor three chiral centers present in the pheromone multistriatin[21], as well as in segments of some polyether antibiotics such as ionomycin[22], lenoremycin[23] and alborixin[24].

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