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STUDIES DIRECTED TOWARD THE SYNTHESIS OF THE EREMANTHOLIDES 1. PREPARATION OF A RING A/B MODEL SYSTEM VIA A CONJUGATE ADDITION-ACYLATION PROTOCOL

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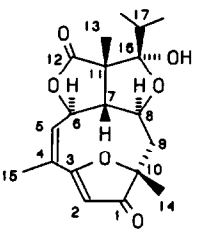
Summary: Synthesis of a model A/B ring subunit of eremantholide A (**1**) is described.

Our interest in the development of a general synthetic protocol for eremantholide A (**1**), a member of a small group of modified germacranolide sesquiterpene lactones isolated by LeQuesne and co-workers, was stimulated both by the significant anti-tumor activity exhibited by **1** and its congeners and the stereochemical issues implicit in a synthetic approach to this novel class of natural substances.[1] Since five of the six chiral centers present in eremantholide A (**1**) reside in the dioxabicyclo[3.3.0]octanone system which comprises the A/B ring subunit of **1**, we initially addressed the problem posed by this stereochemical array by undertaking the construction of the model bicyclic lactone **2** described herein.

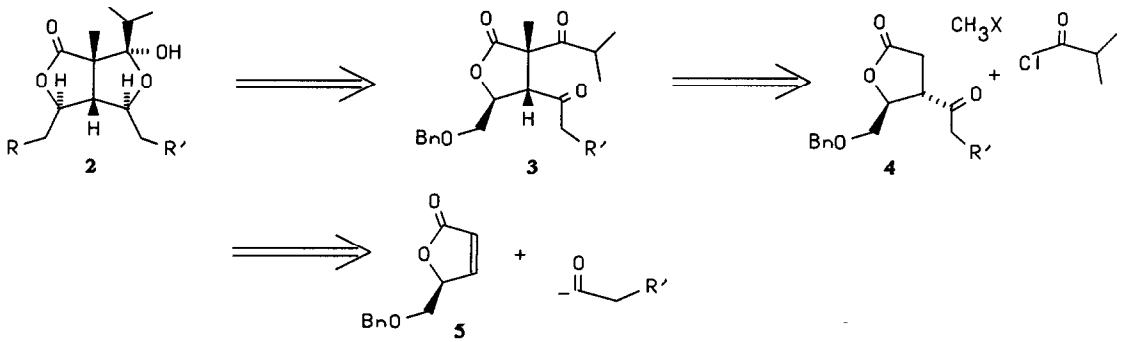


1

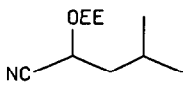
Our retrosynthetic analysis (Scheme 1) of **2** (and **1**) suggests that the relative configuration of the C_{16} center (eremantholide A numbering), a hemi-ketal, is very likely under thermodynamical control (the isopropyl group residing on the less sterically encumbered convex face of the bicyclic system). Thus, we planned to employ ketone **3** as the key precursor to model lactone **2**. Preparation of **3** requires that the α and β sidechains be *cis* disposed on the γ lactone. This arrangement can be readily realized *via* the appropriately ordered sequential introduction of the acyl sidechain and methyl groups at C_{11}.[2] Alkylation of the precursor β-keto ester should afford the desired stereochemistry at C_{11} as the result of the expected introduction of the electrophile *anti* to the sidechain at C_7. The problem is now reduced to the construction of lactone **4** which should be readily accessible *via* conjugate addition of an appropriate acyl anion equivalent *anti* to the C_6 substituent (eremantholide A numbering) in butenolide **5**. Both optical antipodes of **5** are readily available,[3] and conjugate addition of a variety of nucleophiles to **5** has been shown to be highly stereoselective, providing exclusively the desired *trans* adducts.[4] Thus, our

initial goal was to identify one or more acyl anion equivalents which could function in the intended manner.

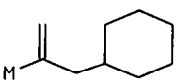
SCHEME 1



A survey of the addition of potential acyl anion equivalents to (∓)**5** was conducted which revealed that only certain systems possessed the correct combination of nucleophilicity and basicity for successful addition.[5,6] We chose to investigate the two most promising methods which were use of protected cyanohydrins and vinyl cuprates (eg. model systems **6** and **7**).



6



7 M= Cu-≡-C_3H_7

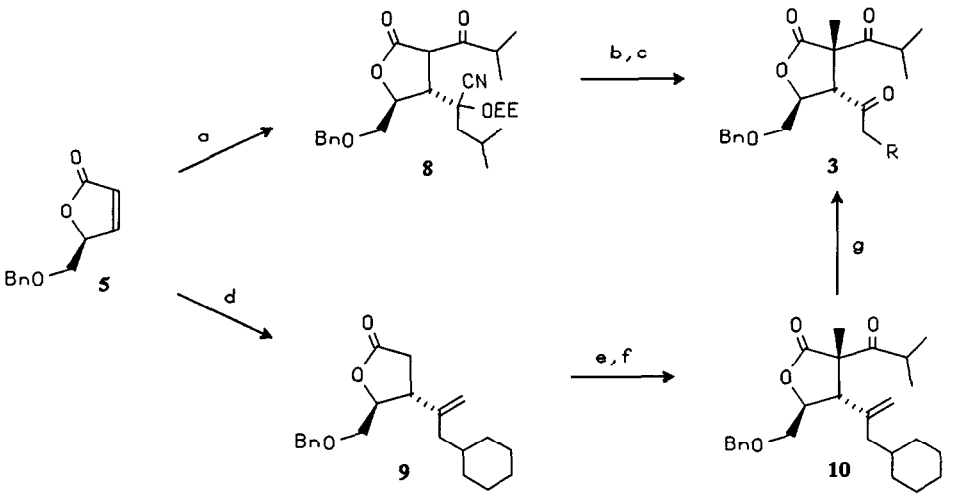
Blocked cyanohydrin **6**, readily available from 3-methylbutanal,[7] upon treatment with LDA was converted to the corresponding lithium anion which smoothly underwent the required conjugate addition to (∓)**5** at -78°C (Scheme 2). The resulting enolate could be trapped *in situ* with isobutyryl chloride to give the protected β-keto lactones **8** which appeared to be a single epimer at C_7 (66%).[8] To introduce the stereochemistry at C_{11}, the mixture of β-keto lactones **8** was then methylated by exposure to NaH/CH_3I in DMF. Deprotection of the resulting mixture of alkylated lactones afforded a single stereoisomeric diketo lactone **3** (R=iPr) in 58% overall yield (from **8**), which confirmed the stereochemical homogeneity of the preceding intermediates at C_7 and C_{11}.[9]

Lactone **3** (R=C_6H_{11}) was also accessible *via* addition of an organocuprate. Exposure of (∓)**5** to the mixed cuprate reagent **7** provided the expected adduct **9** (92%), as a single diastereomer. In this case, the intermediate enolate could not be efficiently trapped *in situ*. However, acylation proceeded smoothly upon treatment of **9** with LDA at -78°C followed by quenching with isobutyryl chloride to afford the expected β-keto lactone (72%). Methylation of this lactone as before with NaH/CH_3I produced a single stereoisomeric alkylated β-keto lactone **10** (87%) which was converted to the analogous diketone **3** (R=C_6H_{11}) *via* ozonolysis in 98% yield.

Completion of our model study now required stereoselective reduction of the C_8 carbonyl group. Unfortunately, attempts to reduce this ketone with a variety of hydride reducing agents under a variety of reaction conditions failed. Apparently the bulky substituents at C_6 and C_{11} render the C_8 ketone effectively inaccessible to nucleophilic reducing agents relative to the other carbonyl groups.[10] However, this problem was readily circumvented by reordering the steps.

Lactone **9** underwent ozonolysis followed by reduction with $NaBH_4$ to afford alcohols **11a** and **11b** (80%) as a 1:1 mixture of C_8 epimers (Scheme 3). No attempt was made to optimize the selectivity of reduction in this model system.[11] The alcohols **11a** and **11b** were separated and both epimers were carried through the remainder of the projected sequence to **2** (R=OBn; R'=C_6H_{11}) at which time the stereochemical assignments for **11a** and **11b** were established (*vide infra*). After protection of the hydroxyl group as the methoxymethyl (MOM) ether by treatment

SCHEME 2[a]



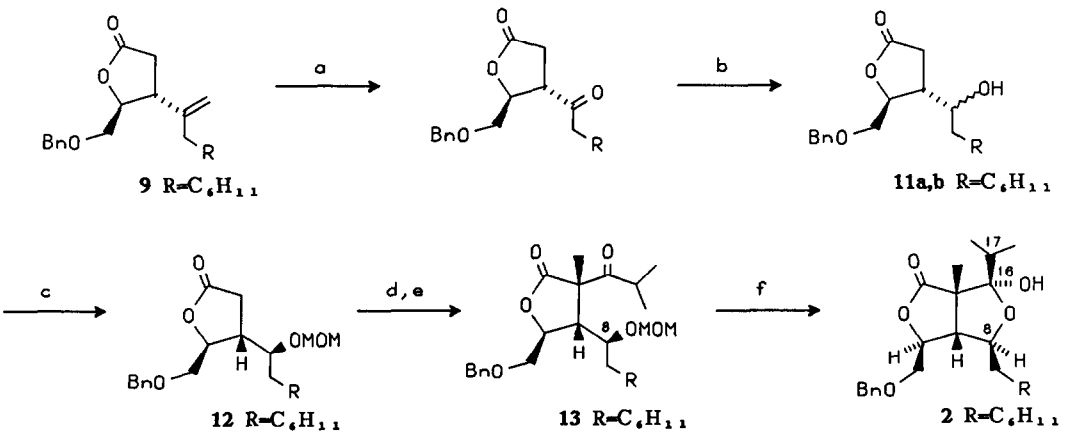
[a]**Reagents:**

a) **6** (1.1 equiv), LDA (1 equiv), HMPA, THF, -78°C then $(CH_3)_2CHCOCl$, -78° → rt, 3h; b) NaH (1 equiv), CH_3I (xs), DMF, 40°C, 16h; c) Amberlyst-15, THF, rt, 12 h, then 5% $NaHCO_3$, rt 3h; d) **7** (2 equiv) , HMPT (4 equiv), Et_2O, -78°C, 2h then **5** and TMSCl (2 equiv) added; e) LDA (2.5 equiv), THF, -78°C, 1h, then $(CH_3)_2CHCOCl$ (3.0 equiv), -20°C, 1.5h; f) NaH (1.5 equiv), CH_3I (xs), THF, 0° → 65°C, 8h; g) O_3 (xs), CH_2Cl_2, -78°C, 0.5h, then $(CH_3)_2S$ (xs), -78°C → rt, 12h.

of **11a**[12] with $CH_2(OCH_3)_2/P_2O_5$ (73%),[13] the resulting lactone **12** was then sequentially C-acylated with isobutyryl chloride and methylated at C_{11} as previously described (Scheme 3) affording β-keto lactone **13** in 56% overall yield (from **12**). Finally, the A/B ring subunit was completed (Scheme 3) by treatment of **13** with TMSBr which selectively cleaved the MOM ether providing the desired lactol **2** (R=C_6H_{11}) in 62% yield.[14]

Confirmation of the structural and stereochemical assignments for **2** (R=C_6H_{11}), and thus **11a** and succeeding intermediates, was obtained from difference NOE studies. Irradiation of the C_{11} methyl group (δ 1.31) of **2**

SCHEME 3[a]



[a]**Reagents:**

a) O_3 (xs), CH_2Cl_2, -78°C, 0.25h, then $(CH_3)_2S$ (xs), -78 → 0°C, 12h; b) $NaBH_4$ (1 equiv), THF-CH_3OH (9:1), 0°C, 0.5h; c) $CH_2(OCH_3)_2$ (xs), P_2O_5, CH_2Cl_2, rt, 6h; d) LDA (3 equiv), THF, -78°C, 1h, then added to $(CH_3)_2CHCOCl$ (6 equiv), 0°C, 2h; e) NaH (1.5 equiv), CH_3I (xs), DMF, -20°C, 4h; f) TMSBr (2 equiv), 4Å Molecular Sieves, THF, -60°C, 30 min.

resulted in an NOE enhancement of the signals for the protons at C_7 (δ 2.41) and the C_{16} isopropyl methine. Furthermore, irradiation of the protons at C_6 (δ 4.60) or C_8 (δ 4.18) resulted in NOE enhancements for the C_8 proton and C_6 protons respectively. These results unequivocally establish the *syn* relationships of the C_7 proton, C_{11} methyl, and C_{16} isopropyl groups as well as the C_6 and C_8 protons fully supporting the structural and stereochemical assignments for **2** (R=C_6H_{11}).

The results of this study have defined a protocol for construction of the eremantholide A/B ring system with a high degree of stereochemical control at 4 of the key stereogenic centers. Efforts are currently underway to apply this strategy to the synthesis of eremantholide A (**1**) itself and the results of these studies will be forthcoming.

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2. For an example of a double functionalization of a butenolide see: Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 7923.

3. Takano, S.; Morimoto, M.; Ogasawara, K. *Synthesis* **1984**, 835, and references therein.

4. a)Tomioka, K.; Ishiguro, T.; Itaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303; b) Hanessian, S. Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170.

5. a) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357; b) Lever, Jr., W. O. *Tetrahedron* **1976**, *32*, 1943.

6. Exposure of **5** to strongly basic anions (eg. dithioacetal anions) resulted in γ deprotonation. Weakly basic anions, such as malonate anions, did not add to **5** due apparently to lack of thermodynamic driving force.

7. Stork, G.; Maldanado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286.

8. Detailed analysis of the ^{1}H NMR was difficult as the result of the presence of diastereomeric mixtures due the chirality at the cyanohydrin center and in the ethoxyethyl protecting group.

9. All new substances exhibited spectroscopic data (IR, NMR, MS) in accord with the assigned structures and satisfactory combustion or high resolution mass spectral analyses. ^{1}H NMR Data (δ at 300 MHz, $CDCl_3$): **2**: 7.30 (m, 5H), 4.60 (d, J=12 Hz, 1H), 4.60 (m, 1H), 4.52 (d, J=12 Hz, 1H), 4.18 (m, 1H), 3.57 (m, 2H), 2.41 (dd, J_1=7 Hz, J_2=3 Hz, 1H), 2.05 (m, 1H) 1.73-0.68 (m, 13H), 1.31 (s, 3H), 1.07 (d, J=7 Hz, 3H), 0.98 (d, J=7 Hz, 3H).

10. For example, treatment of **3** (R=C_6H_{11}) with $LiAl(OtBu)_3H$ resulted in reduction of the γ lactone.

11. In the systems required for **1**, we hoped to utilize chelation control by a β oxygen atom absent in the model systems to effect stereoselective reduction of the C_8 ketone.

12. Only the epimeric series corresponding to **2** (and **1**) is depicted in the interests of clarity.

13. Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

14. Hanessian, S.; DeLorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515. The C_8 epimeric lactone corresponding to **13** underwent facile dehydration to the C_{16}-C_{17} exocyclic enol ether concomitant with deprotection, presumably as the result of steric compression due to the bulky alkyl group at C_8 which resides on the congested concave face of the C_8 epimeric lactol corresponding to **2**.

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