Stereoselective Construction of the Complete Ingenane Ring System

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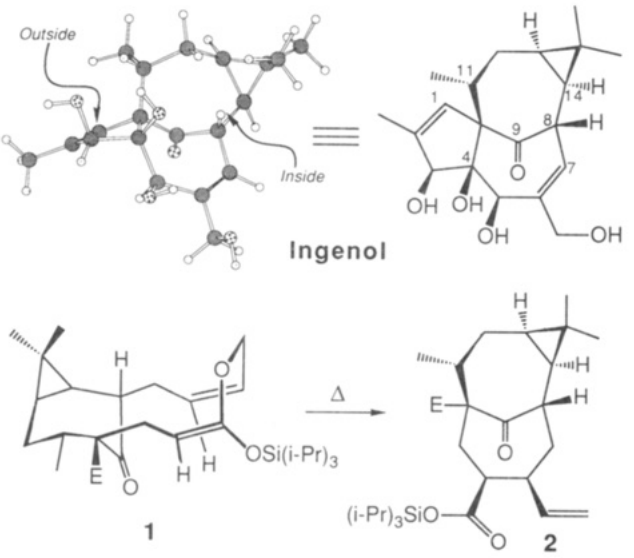
Received June 11, 1993●

Summary: A stereoselective route to the fully assembled and optically pure tetracyclic ring system of ingenol which features a macrocyclic Claisen rearrangement for the construction of the strained *in,out*-bridged bicyclic substructure and simultaneous, strategic placement of functionality has been developed.

Ingenol 3-hexadecanoate is one member of a structurally diverse group of compounds, including the phorbol esters, the teleocidins, and the aplysiatoxins, which are believed to promote tumor formation by activating protein kinase C through binding with a modulatory site, thereby influencing a wide range of biological responses.[1] Several conflicting pharmacophore hypotheses which attempt to develop structural activity relationships for these tumor promoters have been advanced.[2] However, this problem is further complicated by the fact that it is now known that protein kinase C actually comprises a family of at least eight or more closely related isozymes.[3] Nonetheless, the mapping of the tumor promoter pharmacophore by the systematic synthesis of analogs remains a worthwhile goal[4] and could result in the development of new signal transduction-based chemotherapeutic agents.[5] Moreover, it would be highly desirable to discover a "tumor promoter" analog which selectively activates (or inhibits) one or a subset of the PKC subtypes so that its physiological function could be specifically studied.[6]

Ingenol 3-hexadecanoate represents the ideal tumor promoter upon which to launch these investigations. It possesses an extremely rigid carbon skeleton due to the embodiment of a rare example of *in,out*-bridged bicyclic



stereoisomerism. Thus, the biological consequence of functional group deletion and/or modification upon this conformationally restricted template can be more reliably interpreted. We recently reported an effective solution to this challenging stereochemical/strained ring problem by employing a Claisen rearrangement-based ring contraction strategy, cf. $1 \rightarrow 2$ (E = CO_2Me).[7] Unfortunately, the functional groups which emerge following this rearrangement, i.e., the carboxyl and vinyl substituents, are poorly placed for construction of the final A-ring and would require removal of two extraneous carbon atoms for conversion to the C(5) and C(20) hydroxyl substituents, respectively. We report herein a superior macrocyclic Claisen rearrangement which strategically delivers this functionality and permits the first synthesis of the complete tetracyclic ring system with all relevant stereochemistry intact.[8]

Our new route adopts a strategy similar to the one previously employed for controlling the penultimate *in,-out* (*trans*) bridged bicyclic stereochemistry, namely sequential attachment of two functionalized side chains, *trans* to one another, to the enantiomerically pure β-keto ester **3**.[7] Thus, the β-keto ester **3** (E = CO_2Me) was converted to the dianion (2.2 equiv of LDA, 1 equiv of

● Abstract published in *Advance ACS Abstracts,* September 15, 1993.

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(8) For other synthetic approaches, see: (a) Satoh, T.; Kauko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull. Jpn.* **1984**, *32*, 2452. (b) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446. (c) Funk, R. L.; Bolton, G. L. *Ibid.* **1986**, *108*, 4655. (d) Paquette, L.A.; Ross, R. J. *J. Org. Chem.* **1987**, *52*, 5497. (e) Mehta, G.; Pathak, V. P. *J. Chem. Soc., Chem. Commun.*, **1987**, 876. (f) Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192. (g) Wender, P. A.; Lee, H.Y.; Whilhelm, R. S.; Williams, P. D. *Ibid.* **1989**, *111*, 8954. (h) Paquette, L.A.; Shi, Y.-J. *Ibid.* **1990**, *112*, 8478. (i) Rigby, J. H.; Moore, T. L. *J. Org. Chem.* **1990**, *55*, 2959. (j) Winkler, J.; Hong, B.; Bahador, A.; Kazanietz, M.; Blumberg, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 577.

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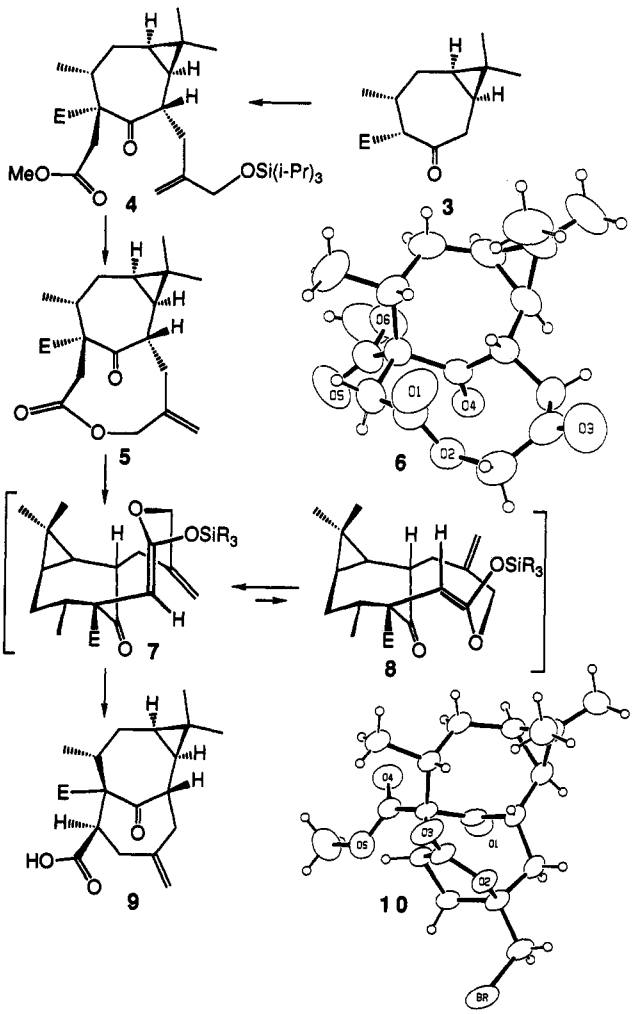
Scheme I



HMPA, THF, −78 to 0 °C, 3.5 h) and alkylated with the triisopropylsilyl ether of 2-(bromomethyl)-2-propen-1-ol[9] (1.5 equiv, −78 to −25 °C, 12 h) to provide a single stereoisomeric product [74%; $[\alpha]^{25}_D$ = 24.1° (*c* 0.22, $CHCl_3$)]. The second side chain was installed in this intermediate by formation of the β-keto ester enolate (NaH, 3 equiv, DMF, 0 °C, 30 min) which was alkylated with methyl bromoacetate (2.5 equiv, 0 °C to rt, 30 min) to afford a single product (85%) assigned the stereochemistry shown in **4**. This stereochemical assignment was verified upon conversion to the Claisen rearrangement substrate, lactone **5**. To that end, the keto diester **4** was desilylated (HF, CH_3CN, 0 °C, 45 min, 86%), selectively saponified (KOH, MeOH, 4.5 h; 91%), and then lactonized using the Keck modification[10] of the Steglich esterification procedure (2 equiv of DCC, 2.5 equiv DMAP, 1.5 equiv of DMAP·HCl, CH_2Cl_2, reflux, 26 h). Since the resulting lactone **5** was obtained as an oil [62%, $[\alpha]^{25}_D$ = +134.5° (*c* 0.60, $CHCl_3$)], it was subjected to ozonolysis (O_3, CH_2Cl_2, −78 °C; Me_2S) to afford the crystalline diketo lactone **6** (mp = 125.5–129.5 °C; 56%) whose structure was solved by X-ray crystallographic analysis.[7] As shown in the ORTEP for **6**, the *in,out*-macrobicyclic [6.4.1] lactone possesses the desired relative stereochemistry, and moreover, the C(7)–C(8)–C(14) bond angle of 111.3° indicates minor bond deformation in comparison to the greater deformation present in ingenol [C(7)-C(8)-C(14) bond angle of 126.5°].

(10) Keck, G. E.; Boden, E. P. *J. Org. Chem.* **1985**, *50*, 2394.

Although the rearrangement of lactone **5**, as the O-silyl ketene acetal **7/8**, was precedented by our previous investigation (**1** → **2**), the facility and stereoselectivity of this transformation was by no means certain since the transition state topologies of these two rearrangement processes are quite different. Thus, all of the atoms participating in the sigmatropy for ketene acetal **1** are within the macrocyclic ring and prefer to rearrange exclusively (predictably) through one of two possible *boatlike* transition state conformers, whereas one sigmatropic atom of the ketene acetal **7/8** is exocyclic to the macrocyclic ring and, consequently, *chairlike* transition states are operative. Moreover, inspection of molecular models as well as molecular mechanics-based[11] transition-state analysis indicated that the diastereotopic chairlike transition states arising from conformers **7** and **8** were of comparable energy. In the event, lactone **5** was converted to a single silyl ketene acetal **7/8** (1.9 equiv of LHMDS, 1 equiv of HMPA, 2.2 equiv of *t*-$BuMe_2SiCl$, 1 equiv of HMPA, THF, −78 to 0 °C, 1 h) which was heated in toluene (95 °C, 3 h) to provide, following hydrolysis of the intermediate silyl esters (HF, CH_3CN, 0 °C), the carboxylic acid **9** [88% from **5**, mp 142.5–145 °C, $[\alpha]^{25}_D$ = +108.9° (*c* 0.88, $CHCl_3$] and its C(4) diastereomer (95:5, respectively). The stereochemical assignment shown for the major rearrangement product, carboxylic acid **9**, was secured by transformation to the bromo lactone **10** (1 equiv of NBS, CH_3CN, 5 min; 55%) whose structure was solved by a single-crystal X-ray crystallographic analysis [C(7)–C(8)–C(14) bond angle = 125.7 °].[17] Therefore, rearrangement through a transition state arising from conformer **7** is highly preferred and may be a consequence of a through-space destabilizing interaction between the ketone and enol ether oxygen atoms in conformer **8**.

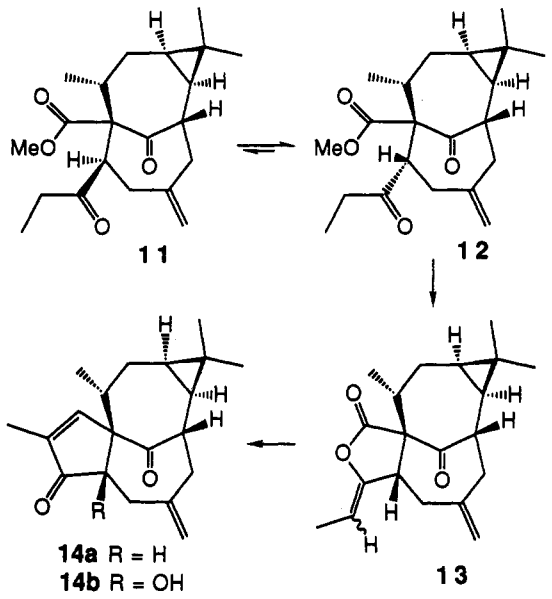
In order to complete the synthesis of the ingenane tetracyclic ring system, epimerization at C(4) of carboxylic acid **9** was required. To this end, carboxylic acid **9** was converted to the ethyl ketone **11** (ClCOCOCl, cat. DMF, benzene, rt, 1 h; 2.3 equiv of EtMgBr, 1.5 equiv of CuI, Et_2O, −78 °C, 30 min; 82% for two steps) which was then subjected to base-catalyzed equilibration[12] (1.1 equiv of NaOMe, MeOH, 25 °C, 3 h) with the epimeric ketone **12** (91% yield of a 1:1 mixture). Having corrected, in part, the stereochemistry at C(4), we investigated strategies for closure of the remaining five-membered ring. We were gratified to discover that the lithium enolate of ketone **12** (1.4 equiv of LHMDS, THF, −78 to −20 °C, 15 min) afforded only the product of O-acylation, enol lactone **13** (2:1 mixture of *Z/E* isomers, respectively; 90%), rather than the anticipated, but less desirable, product of C-acylation.[13] Thus, reduction of the enol lactone **13** with DIBAL[12] (1.2 equiv, toluene, −78 °C) afforded a mixture of cyclic hemiacetals and a keto aldehyde which smoothly cyclized under basic conditions (NaOH, MeOH, 10 min) to afford the aldol adduct **14a** [56% for two steps; $[\alpha]^{25}_D$

(11) We used the MMX program as parameterized, available from Serena Software, 489 Serena Lane, Bloomington, IN 47401. When transition-state bond orders of 0.31 (2.28 Å) for the bond forming and 0.3 (2.13 Å) for the bond breaking were entered, the strain energy for the transition state arising from conformer **8** was calculated to be 0.8 kcal/mol lower than the strain energy for the transition state arising from conformer **7**.

(12) It should be noted that the *in,out*-bicyclo[4.4.1]undecane ring system serves in the capacity of a true "protecting" group for the C(9) carbonyl functionality. Each of the four-atom bridges blocks one face of the carbonyl, and enolization of this carbonyl is precluded by poor alignment of the *inside* C(8) hydrogen atom with the carbonyl π bond.

(13) If the cyclopentane-1,3-dione had been obtained, then the subsequent regiospecific preparation of a vinylogous ester could have been problematic.

Scheme II



= +28.0° (*c* 0.1, $CHCl_3$)].[14] Finally, installation of the C(4) hydroxyl substitutent present in ingenol was then accomplished by conversion of the C(3) carbonyl of diketone **14a**[12] to the corresponding labile trimethylsilyl enol ether (2.5 equiv of TMSCl, 1.5 equiv of Li_2S, 1 equiv Et_3N, CH_3CN, rt, 7 h[15]) and subsequent treatment with *m*-CPBA (1.5 equiv, CH_2Cl_2, 0 °C, 2 h) to afford the diketo alcohol **14b** (37% for two steps).[16]

In conclusion, a viable, stereoselective route to the fully assembled and optically pure tetracyclic ring system of ingenol has been developed. We are now investigating the possibility of incorporating additional functionality into the next generation of Claisen rearrangement substrates for the purpose of introducing the remaining C(5) and C(20) hydroxyl substitutents pursuant to the goal of synthesizing ingenol and/or related analogs.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (Grant No. GM28663).

Supplementary Material Available: Experimental procedures and spectral data for all reaction products (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Support for the stereochemical assignment rests upon irradiation of the resonance assigned to the *inside*, C(8) methine proton at δ 2.91. Nuclear Overhauser enhancements were observed for the C(4), $C(12)_\beta$, and $C(17)_\beta$ proton resonances of 7.7, 14.5, and 15.7%, respectively. Moreover, this experiment suggests that the solution conformer for **14a** is the same as the solid state conformer of ingenol, namely, the C-ring prefers the conformation with an axial C(11) methyl substituent.

(15) Olah, G. A.; Gupta, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272.

(16) The stereochemistry is tentatively assigned based on the expectation that epoxidation of the trimethylsilyl enol ether derivative of ketone **14a** should take place from the less hindered β-face (exo-face) of the bicyclo[5.3.0]decane substructure (fused five- and seven-membered rings).

(17) The author has deposited atomic coordinates for **6** and **10** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.