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NOT THE ENOLATE CLAISEN REARRANGEMENT. A SURPRISING ROUTE TO THE "RIGHT-WING" OF INDANOMYCIN (X-14547A)

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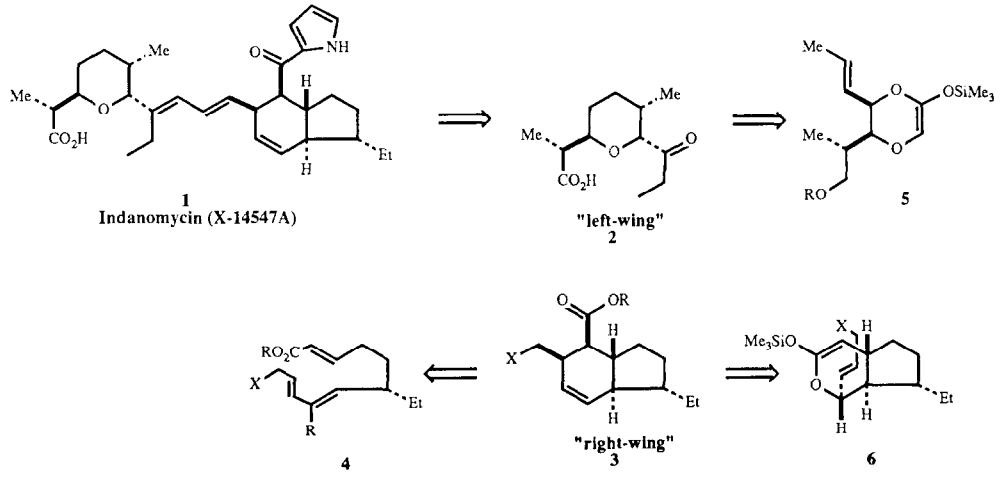
Abstract: A synthesis of the "right-wing" equivalent **22** of the ionophore antibiotic indanomycin is described, wherein an unexpected retro hetero Diels-Alder/intramolecular Diels-Alder pathway gives the desired product of the planned Claisen [3,3]-shift.

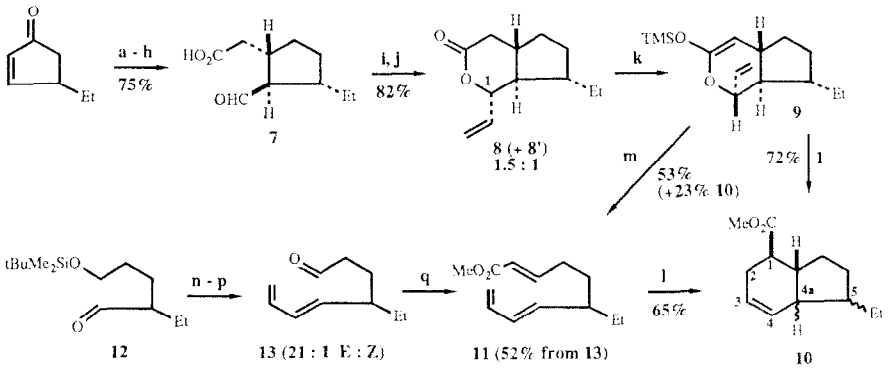
The ionophore antibiotic indanomycin (X-14547A, **1**)[2] can be divided into synthetic subgoals **2** and **3**, respectively described as the "left-wing" and "right-wing". An intramolecular Diels-Alder approach to the hydrindene subunit **3** from a suitable trienoic ester such as **4** has been amply demonstrated.[2m-p] The recognition of **3** as a γ,δ-unsaturated ester suggested that a Claisen rearrangement[3] strategy might provide an alternative route to this "right-wing". Since we had previously developed[4] an efficient synthesis of the "left-wing" hydropyran **2** via a Claisen rearrangement of the silyl ketene acetal **5**, the possibility of assembling each structurally dissimilar subunit **2** and **3** via a common method was attractive.



In accord with available precedent[5] for the lactone enolate Claisen rearrangement in the synthesis of cyclohexene carboxylic acids, the construction of **3** would require that the silyl ketene acetal **6** undergo [3,3] sigmatropic reorganization via a boat-like transition state, as shown. However, the precedent did not extend to bicyclic systems with a *trans*-fused cyclopentane ring, and examination of molecular models of **6** revealed that even modest pericyclic overlap would entail substantial ring strain. Thus, a somewhat simpler system than **6** was initially chosen to test the feasibility of this questionable step.

In a pedestrian but high-yielding sequence of reactions, 4-ethylcyclopentenone[6] was converted to the aldehyde **7** (Scheme I). Addition of this aldehyde to excess vinylmagnesium bromide in tetrahydrofuran (THF) at -78°C gave in 85% yield a mixture of allylic alcohols. Lactonization[7] with dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) provided in 96% yield the C(1)-epimeric δ-lactones **8** (mp 36-38°C) and **8'**, separable by flash chromatography,[8] in a ratio of 1.5:1.

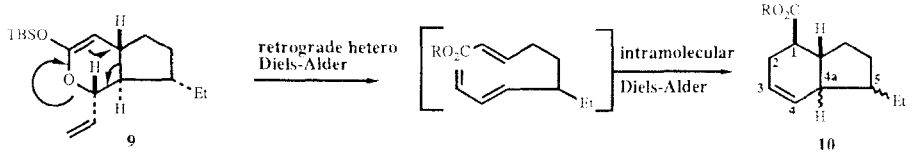
SCHEME I[19]



(a) $(H_2C=CH)_2CuLi$, THF, -78°C; $BrCH_2CO_2t$-Bu, HMPA, -78 → 0°C. (b) $LiAlH_4$, THF, -78 → 25°C. (c) t-$BuPh_2SiCl$, DMF, imidazole, 25°C. (d) MsCl, DMAP, Et_3N, CH_2Cl_2, 0 → 25°C. (e) $LiEt_3BH$, THF, reflux. (f) n-Bu_4NF, THF, 25°C. (g) $H_2Cr_2O_7$, aq. acetone, 25°C. (h) O_3, 1:1 CH_2Cl_2-MeOH, -78°C. (i) $H_2C=CHMgBr$, THF, -78°C. (j) DCC, DMAP, CH_2Cl_2, 0 → 25°C.[7] (k) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, -100 → 25°C; remove THF *in vacuo*, add $PhCH_3$. (l) 135°C, 20 h; aq. HCl; CH_2N_2, Et_2O, 0°C. (m) 95-100°C, 5 h; aq. HCl; CH_2N_2, Et_2O, 0°C. (n) $Ph_2P(O)CHLiCH=CH_2$, THF, -78 → 25°C.[20] (o) n-Bu_4NF, THF, 25°C. (p) $CrO_3 \cdot 2$ pyr, CH_2Cl_2, 0 → 25°C. (q) Ph_3PCHCO_2Me, CH_2Cl_2, 25°C

Conversion of lactone **8** to the trimethylsilyl ketene acetal **9**[9] and thermolysis thereof in toluene at 135°C (bath temperature) gave in 72% yield the hydrindene nucleus **10** as a mixture of four diastereomers (31:9:5:1).[10] The major product [α-H at C(4a), α-Et at C(5)] was that expected from a Claisen [3,3]-sigmatropic reorganization of **9**. However, the formation of additional diastereomers was indicative of another pathway, revealed by conducting the thermolysis under milder conditions (95-100°C, 5 h).[11] In addition to the hydrindenes **10** (23%), there was isolated the *E,E*-triene **11** in 53% yield. Resubjection of **11** to thermolysis at 135°C for 20 h gave in 65% yield the hydrindene mixture **10**. Confirmation of the structure of triene **11** was accomplished by independent synthesis from aldehyde **12**[2m,o] via dienal **13** as shown.

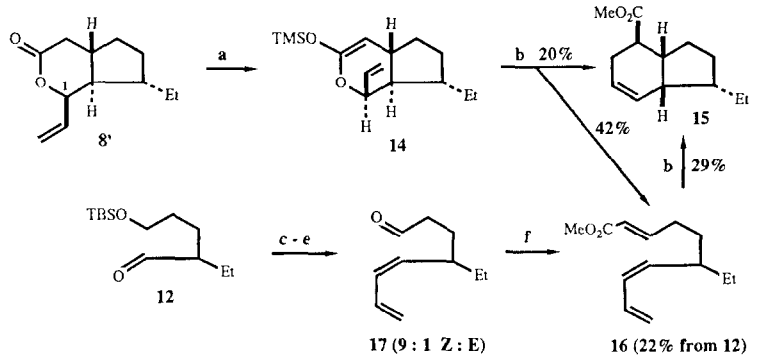
It was thus apparent that a retrograde hetero Diels-Alder reaction was preempting the desired [3,3]-shift, but that a subsequent intramolecular Diels-Alder[12] process of higher activation energy led to the expected product [C(4a) α-H, C(5) α-Et] as the major diastereomer (eq. 1). The presence of the three minor cycloadducts was a consequence of the imperfect stereoselectivity of the Diels-Alder conversion to **10**.[13]



(1)

As shown in Scheme II, similar results were obtained upon thermolysis of the silyl ketene acetal **14** derived from **8'**. In this case a single hydrindene, to which we assign structure **15**,[14] was produced (20%) in addition to the *E,Z*-triene **16** (42%). The high stereoselectivity in the Diels-Alder stage of this cycloreversion/cycloaddition is attributable to the relative unreactivity of the triene **16**.[15] The structure of **16** was confirmed by independent synthesis from **12** as shown, and thermolysis of this material gave the same hydrindene as had **14** under like conditions.

SCHEME II[19]

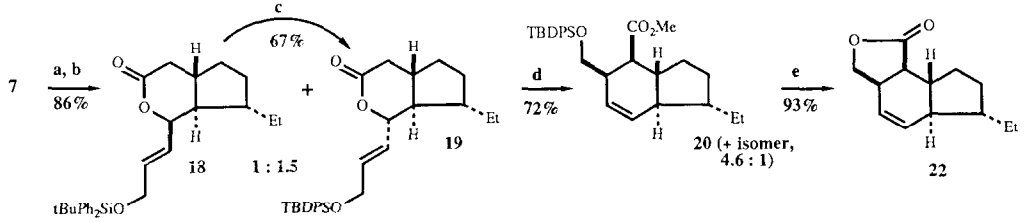


(a) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, -100 → 25°C; remove THF *in vacuo*, add $PhCH_3$. (b) 135°C, 20 h; aq. HCl; CH_2N_2, Et_2O, 0°C. (c) $Ph_2PCHLiCH=CH_2$, $Ti(Oi\text{-}Pr)_4$, THF, -78°C; MeI, -78 → 25°C.[20] (d) *n*-Bu_4NF, THF, 25°C. (e) $CrO_3 \cdot 2$ pyr, CH_2Cl_2, 0 → 25°C. (f) Ph_3PCHCO_2Me, CH_2Cl_2, 25°C.

Our doubts about the viability of the Claisen rearrangement route to the "right-wing" of indanomycin had thus been confirmed. However, the intervening tandem sequence of retro hetero Diels-Alder/intramolecular Diels-Alder reactions gave the desired product in the model conversion (**8** → **10**). Therefore, the intended application was pursued.

Addition of (*E*)-3-bromomagnesio-1-*t*-butyldiphenylsiloxy-2-propene[16] to the aldehyde **7** gave a mixture of hydroxy acids (94%) which, upon lactonization with DCC/DMAP,[7] gave a 91% yield of the separable lactones **18** and **19** (mp 79-80°C) in a ratio of 1:1.5 (Scheme III).[17] The minor, undesired isomer **18** was converted to **19** by hydrolysis and relactonization by the Mitsunobu procedure[18] in 67% overall yield. Conversion of **19** to the trimethylsilyl ketene acetal[9] and thermolysis in toluene at 135°C (bath temperature) for 24 h gave, following hydrolysis and esterification, a 72% yield of the known,[2o] *trans*-fused hydrindene **20** and a separable diastereomer in a ratio of 4.6:1. Removal of the silyl protecting group with *n*-Bu_4NF as previously described[2o] proceeded with lactonization to give in 93% yield the known "right-wing" synthon **22** (mp 68-69°C; lit. 68-68.5°C,[2o] 67.5-68.5°[2m]), identical with that described by Nicolaou[2o] and by Ley.[2m] The overall yield for the production of **22** from 4-ethylcyclopentenone exceeds 20%. This work, when combined with previous efforts from our labs[4] and others,[2m,o] constitutes a formal total synthesis of indanomycin (X-14547A, **1**).

SCHEME III[19]



(a) (*E*)-*t*-$BuPh_2SiOCH_2CH=CHMgBr$,[16] THF, -78°C. (b) DCC, DMAP, CH_2Cl_2, 0 → 25°C.[7] (c) LiOH, aq. THF, 25°C; 5% aq. HCl; DEAD, Ph_3P, $PhCH_3$, -20°C.[18] (d) LDA, Me_3SiCl, Et_3N, THF, -100 → 25°C; remove THF *in vacuo*, add $PhCH_3$; 135°C, 24 h; aq. HCl; CH_2N_2, Et_2O, 0°C. (e) *n*-Bu_4NF, THF, 0°C, 2.5 h.[2o]

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