

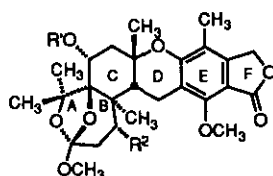
A UNIFIED SYNTHETIC STRATEGY FOR ELABORATION OF THE DEF TRICYCLIC SUBUNIT COMMON TO THE AUSTALIDE MYCOTOXINS[‡]

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Abstract - Tricycle (19), representing the DEF subunit common to all known austalide mycotoxins, has been economically synthesized from 2,3-dihydropyran in 8 steps via several highly stereo- and regioselective transformations.

The extensive investigation of those toxigenic agents produced by various strains of *Aspergillus ustus* undertaken by Horak, Steyn, Vleggaar, and their associates was responsible for the discovery more than 10 years ago of the structurally unique meroterpenoid metabolites austalide A-E (1-5).² In

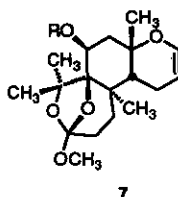


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|------------------------------------|-----------------------------------|
| 1, A: R' = Ac R ² = H | 4, D: R' = H R ² = OAc |
| 2, B: R' = H R ² = H | 5, E: R' = Ac R ² = OH |
| 3, C: R' = Ac R ² = OAc | 6, F: R' = H R ² = OH |

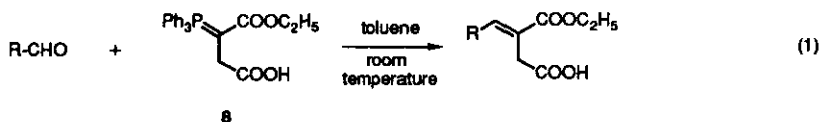
1985, the South African team also reported the identification of austalides F (6)-L.³ The molecular architecture contained in rings D, E, and F of 1-6 is common to all members of this mycotoxin family. Although the biosynthesis of the austalides is believed to involve the cyclization of 6-[(2E,6E)-farnesyl]-5,7-dihydroxy-4-methylphthalide, the key biogenetic precursor to mycophenolic acid,⁴ the distinctive

[‡]This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

DEF array was viewed to be an attractive forum for the development of new multiple annulation schemes capable of rapidly assembling the pyran/*p*-cresol/butenolide triad. A number of earlier attempts at meeting this challenge^{5,6} have, however, not resulted in the successful production of this heterocyclic network. Herein, we describe a concise means for constructing this ring system that holds the prospect for direct adoption in the total synthesis of austalides A-F.



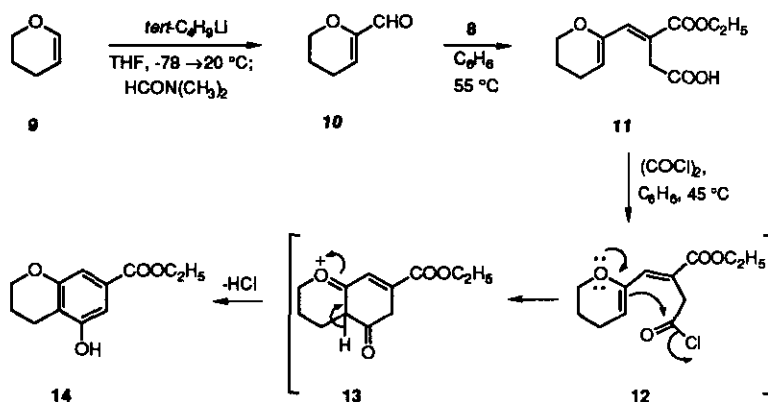
Our retrosynthetic planning was designed with a long-range view to utilizing 3,4-dihydro-2*H*-pyran (**9**), since tetracyclic ABCD subunits such as **7** have already been readily assembled in this laboratory.⁶ To this end, **9** was lithiated⁷ with *tert*-butyllithium in THF (highly concentrated solutions are mandatory) and treated with DMF⁸ to give aldehyde (**10**) (Scheme I). Despite the ready availability of the multifunctional Wittig reagent (**8**) from maleic anhydride, triphenylphosphine, and ethanol,⁹ only one report has described its use for the synthesis of 3-alkylidenesuccinic acid monoethyl esters.¹⁰ The work of Röder and Krauss is noteworthy because they established that the process positions the R group of the aldehyde *cis* to the acetic acid substituent in highly stereoselective fashion as illustrated in eq. (1).



The condensation of purified **8** with **10** was examined under a variety of conditions. As seen in Table I, the use of benzene at 55 °C made possible the acquisition of **11** in yields invariably in excess of 89%. The stereochemical homogeneity of **11** was evident upon inspection of its ¹H and ¹³C nmr spectra.¹¹ The indicated *E* configuration was corroborated by facile and direct conversion to **14**.

In routine experiments, **11** was subjected to flash chromatography and treated in turn with oxalyl chloride (1.5 equiv.) in CH₂Cl₂ at the reflux temperature. These conditions resulted in spontaneous ring closure and formation of the bicyclic phenol (**14**) (77%). This smooth cyclization is believed to be

Scheme I



mediated by intramolecular nucleophilic attack on the electrophilic acid chloride by the proximal vinyl ether functionality as in **12**. Once oxonium ion (**13**) is formed, the development of aromatic character serves as an unavoidable thermodynamic driving force.

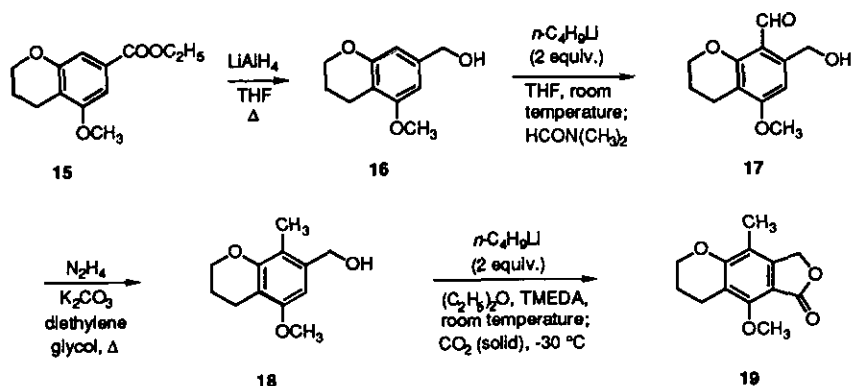
Table I. Conditions Examined for the Wittig Condensation of **8** with **10**.

solvent	temperature ($^\circ\text{C}$)	ratio 8 : 10	reaction time, days	yield (%)
toluene	40	0.95	3	40
benzene	50	1.00	2	76
benzene	20	1.01	9	64
benzene	55	1.01	1.5	≥ 89

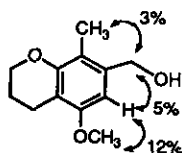
With the acquisition of **14**, fully regiocontrolled introduction of an arylmethyl substituent and the carbonyl group of the butenolide was now called for. In view of our recent discovery of the remarkably disparate manner in which methoxyl oxygens and cyclic ether oxygens control the regiochemistry of aryl lithiation,¹² **14** was *O*-methylated (NaH , CH_3I) to give **15** (70%) and subsequently reduced to the benzyl alcohol (**16**) (94%, Scheme II).

In a further reflection of the greater directing power of the pyran oxygen, sequential exposure of **16** to

Scheme II



n-butyllithium in benzene at room temperature and then to DMF afforded exclusively the rather sensitive aldehyde (**17**) (69%). When the Wolff-Kishner reduction of **17** was performed immediately, colorless crystalline **18** was obtained with 60% efficiency. NOE studies performed on this stable intermediate (see illustration) confirmed that the requisite isomer was in hand. Finally, the lactone ring in target molecule (**19**) was secured by lithiation of intermediate (**18**) with *n*-butyllithium in ether containing TMEDA and ensuing carboxylation with solid CO₂. The yield of this step was 60% based on recovered starting material.



To sum up, a direct route to **19** has been developed that capitalizes on initial aryl annulation of **10** via **8** and culminates with completely regiocontrolled functionalization of the benzene ring in this intermediate. Progress towards the enantiospecific total synthesis of members of the australide family will be reported in due course.

ACKNOWLEDGMENT

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11. For **11**: ^1H Nmr (300 MHz, C_6D_6) δ 7.19 (s, 1 H), 4.80 (t, $J = 4.2$ Hz, 1 H), 4.08 (s, 2 H), 4.00 (q, $J = 7.0$ Hz, 2 H), 3.53 (t, $J = 5.0$ Hz, 2 H), 1.60 (m, 2 H), 1.20 (m, 2 H), 0.96 (t, $J = 7.0$ Hz, 3 H); ^{13}C nmr (75 MHz, C_6D_6) ppm 178.2, 167.7, 151.7, 136.6, 122.6, 112.5, 65.7, 61.0, 33.5, 21.6, 21.4, 14.1.
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