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TOTAL SYNTHESIS OF (±)-12-NORALLIACOLIDE, (±)-ALLIACOL A AND (±)-ALLIACOLIDE

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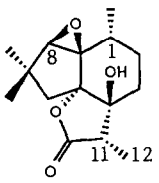
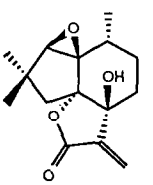
Abstract: The title compounds were prepared via a "one-pot" γ-lactone annulation sequence in which dilithium acetate functions as a bis-nucleophile, first at carbonyl and then at hindered allylic sulfonate centers (S_N' orientation).

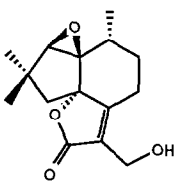
The alliacolides (exemplified by 1-3, below), produced by the basidiomycete Marasmius alliaceus, are novel epoxy-lactones[1] which may originate biosynthetically from cadinane precursors.[2]



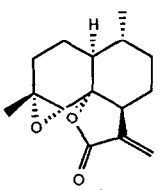
1 ALLIACOLIDE



2 ALLIACOL-A



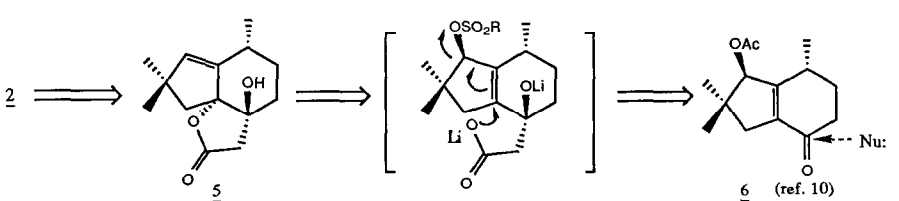
3 ALLIACOL-B



4

Arteannuin B (4) and the alliacolides are quite unusual among the various types of sesquiterpene lactones[3] in that tertiary hydroxyl groups, rather than primary or secondary ones, are intramolecularly γ-lactonized. We met this challenge in a recently completed total synthesis[4a] of 4 by using a mechanism-based intramolecular conjugate reduction designed to culminate in a trans-fused γ-lactone.[4b] This Letter reports a novel and expedient method for β-oxo-γ-butyrolactone cis-annulation,[5] which is especially relevant for synthesis of alliacolides such as alliacol A (2).[6]

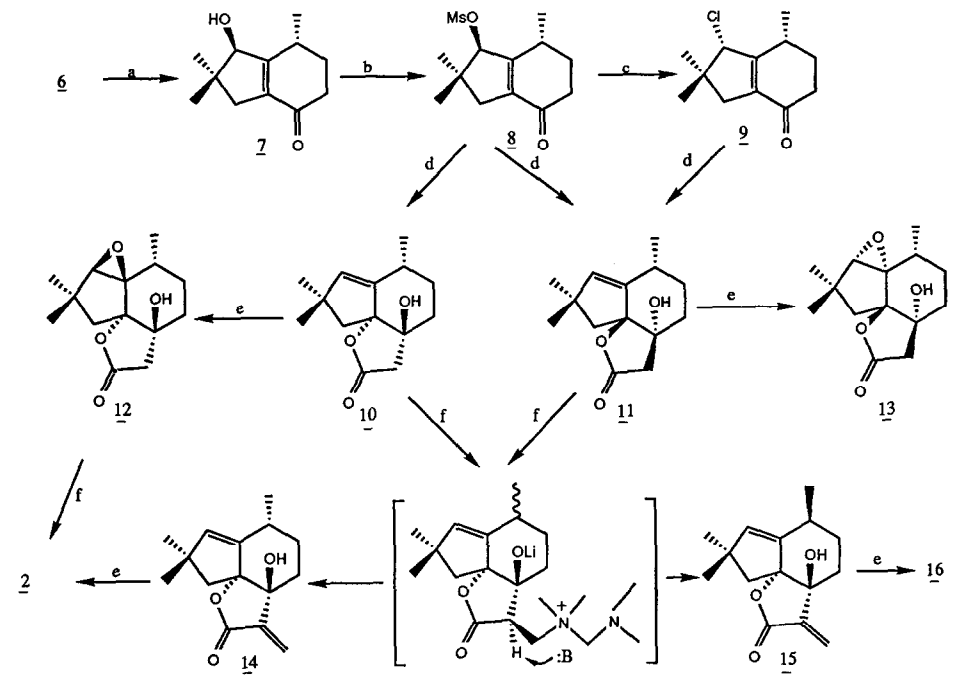
Our strategy is based on fully exploiting both nucleophilic sites of dilithium carboxylates[7] in a "one-pot" sequence. Ordinarily, the initially-formed carboxylate ion (pK_a ~5) functions only to enhance the nucleophilicity of the dianion[7] (pK_a ~24), even when bis-electrophiles are the reaction partners.[8] In the present investigation, we envisioned attack first by the "α-carbanion" of dilithium acetate (DILA) at an unhindered carbonyl group, followed by intramolecular carboxylate closure to 5 (S_N' orientation, probably via ion pair collapse[9]), although a labile vinyl epoxide might first intervene. Whatever the exact mechanistic details,



5 6 (ref. 10)

the ring-forming step was expected to be competitive with further bimolecular DILA attack at the hindered neopentyl center in the first-formed adduct.

Previous synthetic approaches[6] to the alliacolides did not solve the stereochemical problem arising from the cis-relationship of the C-1 methyl group and the γ-lactone ring. In both cases,[6] C-1 epimers predominated. To produce 5, DILA attack has to occur from the more hindered side of the conformationally-mobile cyclohexenone ring, cis to the non-adjacent methyl group. The prospects for achieving at least random diastereoselectivity (ie. 50:50 epimer ratio) are not further diminished if the leaving group introduced into 6[10] remains trans to the C-1 substituent (to "balance" remote steric hindrance). This necessity was confirmed in the two-stage DILA addition to γ-chloro-α,β-unsaturated ketone 9,[11] unintentionally obtained, with net inversion at C-8, from 7 and methanesulfonyl chloride in pyridine. As shown below, 9 produced only the C-1 epimeric precursor 11 in 80% yield (due to cumulative backside steric hindrance from both C-1 and C-8 substituents). Accordingly, we carefully reacted 7 with sulfene[12] and immediately carried out inverse DILA addition to crude 8 without isolation or purification. Upon workup, an



Reagents and conditions: a) K_2CO_3, MeOH, 25°, 12h; b) 1.5 eq. MsCl, 2 eq. Et_3N, THF, 25°, 30 min; c) 1.5 eq. MsCl, pyridine, 25°, 12h (from 7);d) 3.5 eq. DILA, hexane-THF, 3.5 eq. HMPA, 25°, 12h; e) 1.5-2.0 eq. MCPBA, CH_2Cl_2, $NaHCO_3$, 25°, 3h; f) 3 eq. LiTMP, THF-HMPA, -20°, Eschenmoser's salt, -20°→25°, 12h.

inseparable 1:1 mixture of lactones 10 and 11 ($\nu_{C=O}$ 1770 cm^{-1}) was obtained (45-50% reproducible yield), along with some acidic by-products that were not further characterized. NMR integration of the C-8 vinyl hydrogen signals at 5.63 ppm (singlet, $J_{1,8}$=0 Hz) in 10 and 5.55 ppm (doublet,

$J_{1,8}$=2.0 Hz) in 11 established the isomer ratio and configurational assignments, based on the above long-range coupling constants.[6b] Hydroxyl-assisted epoxidation[13] of 10 and 11 afforded, in combined 97% yield, 12-noralliacolide (12), mp 160-161°, whose ^{1}H and ^{13}C NMR spectra were in full agreement with reported values,[1c] and 1-epi-12-noralliacolide (13), mp 172-173°. The C-10 methyl group in 13 is shielded by the neighboring oxirane ring (δ_{CH_3} 0.76 ppm in ^{1}H spectrum and 14.21 ppm in ^{13}C), an effect also noted by Pattenden[6b] in several other 1-epi-alliacolide compounds.

With the five chiral centers in 12 correctly in place, only α-methylenation of the γ-lactone ring remained to be completed enroute to alliacol A. We had planned to use Danishefsky's protocol[14] which was designed for hydroxy-γ-lactones without hydroxyl protection-deprotection stages, a welcomed prospect with our labile and hindered tertiary hydroxyl substituent at C-4. Lithium tetramethylpiperidide was found to be most efficient for deprotonating 12 at C-11 (first C_4-OH), after which we added excess N,N-dimethylmethyleneammonium iodide (Eschenmoser's salt). Unexpectedly,[14] alliacol A was formed directly (45%), without requiring addition of methyl iodide to quaternize the tertiary amine group prior to base-induced elimination. Apparently, Eschenmoser's salt can serve the dual purpose of C-11,12 carbon-carbon bond formation and nitrogen quaternization in this instance (see chart). (±)-Alliacol A (2), mp 164-165°, was fully characterized by ^{1}H and ^{13}C NMR, as well as IR and mass spectroscopy, using the data of Hanson[1c] and Steglich[1d] for comparison. In addition, hydrogenation of 2 over Pd-C gave alliacolide (1) as reported,[1d] allowing us to verify the identity of our (±)-1[15] with a sample of natural (-)-1 provided by Professors Hanson and Thaller. Finally, an alternative procedure to obtain 2 was found to be more convenient than prior separation of 12 from 13; direct methylenation[14] of the 10 and 11 epimeric mixture with Eschenmoser's salt gave a 1:1 mixture (45% yield) of α-methylene-γ-lactones 14 and 15 ($\nu_{C=O}$ 1750 cm^{-1}). As before, epoxidation led to separable 2 and comparable amounts of 1-epi-alliacol A (16) mp 150-152°.

The total synthesis of 12-noralliacolide (12) requires only eleven steps beginning with cyclopentenone.[10] Versatile "one-pot" reactions of note are the ceric ammonium nitrate oxidative hydrolysis of saturated dithianes to conjugated ketones[10] and the doubly-nucleophilic DILA annulation leading to cis-fused β-oxo-γ-butyrolactones. Clearly a variety of alliacolides, in addition to 1 and 2, can be prepared expeditiously by this approach.

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5. For other relevant methodologies, see M. J. Begley, M. Ladlow and G. Pattenden, J. Chem. Soc. Perkin I, 1095 (1988) and references cited therein.
6. a) First approach to alliacol B: R. A. Rapheal and S. J. Telfer, Tetrahedron Lett., 26, 489 (1985).
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c) Reviews: N. Petragnani and M. Yonashiro, Synthesis, 521 (1982). E. M. Kaiser, J. D. Patty and P. L. A. Knutson, Synthesis, 509 (1977). DILA has been used in a number of instances to form γ-lactones (e.g. from epoxides and α-hydroxyketones). However, only the first step is based on DILA nucleophilicity; lactonization is then achieved by acid-catalyzed hydroxy attack at the protonated carboxyl group.
8. For example, Creger (ref. 7a) reports the high-yield formation of α,ω-diacids from 1,3-dibromopropane and 1,4-dibromobutane with dilithium isobutyrate (2 eqs) and not lactones (or β-ketoacids derived therefrom).
9. Although S_N2' reactions usually proceed with overall syn-stereochemistry (cf. R. M. Magid, Tetrahedron, 36, 1901 (1980)), examples of anti-S_N2' reactions are also documented (cf. E. J. Corey and A. V. Gavai, Tetrahedron Lett., 29, 3201 (1988) and refs. cited). However, with the weakly basic nucleophile R-COO$^-$, bond formation probably occurs after sulfonate ionization (i.e. ion pair collapse), presumably without stereochemical preference (cf. F. G. Bordwell, A. H. Clemens and J-P Cheng, J. Am. Chem. Soc., 109, 1773 (1987) and refs. cited).
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11. All new compounds, including epimeric mixtures, were thoroughly characterized by an appropriate combination of IR, ^{1}H and ^{13}C NMR and mass spectroscopy (EI or CI); elemental compositions were determined by HRMS. Salient information on specific compounds is given below:
7: IR($CHCl_3$) 3425, 1650 cm^{-1}; ^{1}H NMR(300 mHz, $CDCl_3$) δ 4.31 (d,1H,J=5 Hz), 1.12 (d,3H,J=6 Hz), 1.04 and 0.94 (s,6H); ^{13}C NMR(75 mHz, $CDCl_3$) δ 199.89, 166.90, 136.33, 84.85, 41.93, 41.86, 36.09, 31.33, 28.80, 22.77, 22.34, 17.94; MS(EI) m/z 194 (M^+), 179, 151 (base peak).

12: IR($CHCl_3$) 1780 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 3.18 (s,1H), 2.75 and 2.52 (2H, AB quartet, J=15 Hz), 2.00 and 1.28 (2H, AB quartet (J=15 Hz), 1.10 (d,3H,J=6 Hz), 1.08 (s,6H); ^{13}C NMR ($CDCl_3$) δ 174.07, 94.61, 75.81, 69.05, 68.37, 43.05, 41.60, 38.97, 35.53, 31.59, 26.01, 24.45, 24.11, 18.18; HRMS, calcd. for M^+ m/z = 252.1361, found m/z = 252.1357.

13: IR($CHCl_3$) 1780 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 3.27 (s,1H), 2.64 and 2.45 (2H, AB quartet, J=15 Hz), 2.01 and 1.30 (2H, AB quartet, J=15 Hz), 1.11 and 1.07 (s,3H each), 0.76 (d,3H,J=7 Hz); ^{13}C NMR($CDCl_3$) δ 173.90, 92,40, 75.20, 69.00, 68.72, 44.16, 41.26, 38.03, 35.70, 27.49, 26.79, 24.51, 24.15, 14.21; MS (EI), m/z 252 (M^+), 237, 210, 193, 182 (base peak).

2: IR($CHCl_3$) 1761 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 6.36 (s,1H), 5.90 (s,1H), 3.19 (s,1H), 1.88 and 1.21 (2H, AB quartet, J=14.1 Hz), 1.13 and 1.09 (s,6H), 1.11 (d,3H,J=6.9 Hz); ^{13}C NMR($CDCl_3$) δ 168.79, 142.98, 124.72, 95.02, 76.69, 69.53, 67.22, 41.79, 39.33, 38.69, 31.61, 26.39, 24.49, 24.15, 19.40; HRMS, calcd. for M^+ m/z = 264.1362, found 264.1366.

16: IR($CHCl_3$) 1765 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 6.14 (s,1H), 5.69 (s,1H), 3.24 (s,1H), 1.87 and 1.18 (2H, AB quartet, J=13.8 Hz), 1.07 (s,6H), 0.78 (d,3H,J=6.6 Hz; ^{13}C NMR($CDCl_3$) δ 168.70, 144.02, 120.31, 92.43, 76.72, 68.81, 68.10, 41.65, 38.12, 36.73, 27.48, 26.25, 24.55, 24.15, 14.52; MS (EI) 264 (M^+), 249, 236, 193, 151.
12. R. K. Crossland and K. L. Servis, J. Org. Chem., 35, 3195 (1970).
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14. S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. Etheridge, J. Am. Chem. Soc., 99, 6066 (1977).
15. Methylation of the dianion from 12 produces 11-epi-alliacolide instead of 1, an outcome not rectifiable by C-11 reionization-protonation (3 eq. LITMP, then HOAc). Furthermore, the addition of dilithium propionate to 8 did not prove to be a practical route to 8,9-deoxy-1.

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