Tetrahedron Letters, Vol. 34, No. 28, pp. 4431-4434, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

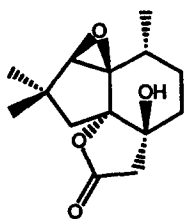
A STEREOSELECTIVE TOTAL SYNTHESIS OF ALLIACANE LACTONES

by Peter T. Lansbury* and James J. La Clair

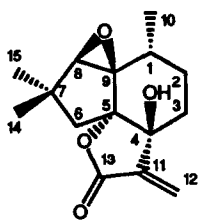
Department of Chemistry
State University of New York at Buffalo
Buffalo, NY 14214

Abstract: Sesquiterpene lactones of the alliacane type have been synthesized for the first time with complete stereocontrol during enolate addition to hydrindenones and intramolecular S_N' cyclizations onto allylic chloroacetates.

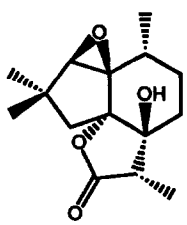
A key step in our first synthesis[1] of 12-noralliacolide (1), alliacol A (2), alliacolide (3) was direct lactonization of a γ-mesyloxy-α,β-unsaturated ketone **5** with dilithium acetate, a process in which the latter acted as a dual nucleophile. Although this tandem annulation provided intermediate **6** expeditiously, the isolation of comparable amounts of epimer **7** detracted from the optimal goal (**6**»**7**). Moreover, the formation of enone **5**



12-Noralliacolide (1)

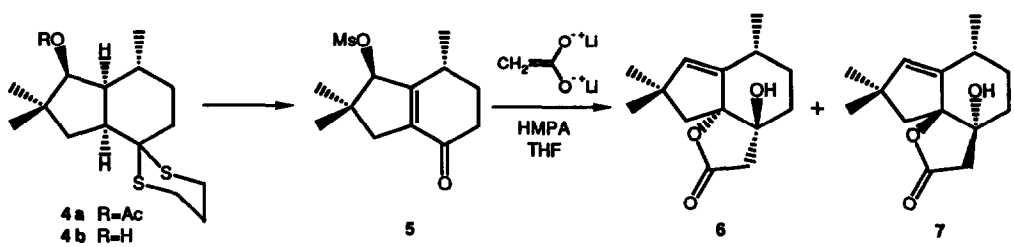


Alliacol A (2)



Alliacolide (3)

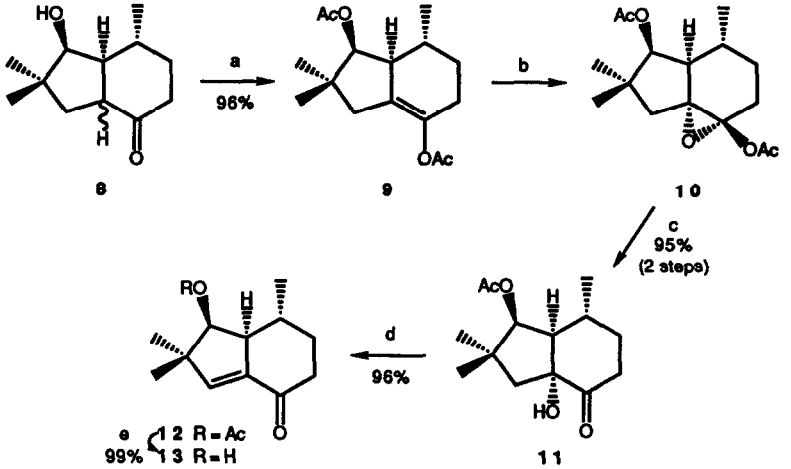
precursors, *via* direct ceric ion oxidation[3] of hydrindanone dithiane derivative **4a** was accompanied by irreversible loss of more than half of the bicyclic template when the conjugate double bond was unveiled. We therefore set out to remedy these two selectivity problems, especially generation of the required stereochemical relationship of carbon substituents at C-1 and C-4 (*cis* in **6** or equivalent structures). In the course of solving this challenging problem[1,4,5], the wasteful aspects of the **4**→**5** transformation have also been eliminated. Described herein is a high-yielding linear synthesis of 12-noralliacolide (1) which proceeds with total regio- and stereoselectivity.



4a R=Ac
4b R=H

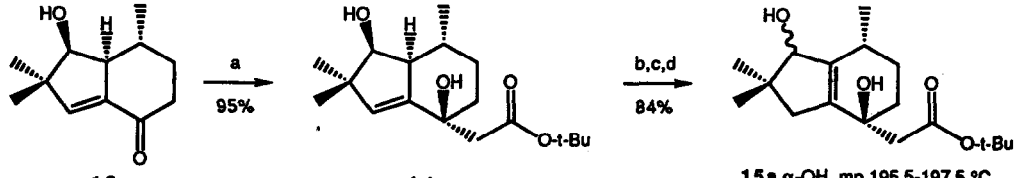
5 **6** **7**

When dithiane **4b**[6,7] was carefully unmasked with trimethyloxonium tetrafluoroborate, the resulting saturated hydrindanone **8**, mp 94-6 °C (~5:1 *cis* : *trans* mixture), was converted to a single enol acetate **9** that underwent stereoselective epoxidation to **10**. Epoxide opening (**10**→**11**) and acid-catalyzed α-hydroxyketone dehydration (regioselective, *via* an *anti* elimination of H_2O) afforded enone **12** in high yield (87% from **8**).



Reagents: (a) Ac_2O, cat. 70% $HClO_4$, CCl_4, C_6H_6, 0 to 25 °C. (b) m-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 3 h. (c) 0.05 M KOH in H_2O, CH_3OH, CH_2Cl_2, 1 h. (d) p-TsOH, MsCl (1.25 eq), C_6H_6, 25 °C, 1.5 h. (e) K_2CO_3, H_2O, CH_3OH.

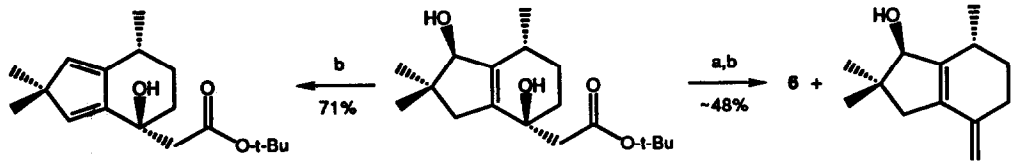
Carbon nucleophiles such as allylmagnesium chloride and a variety of acetate ester enolates react with **12** or the deacylated hydroxyenone **13** almost exclusively from the α-side, without detectable amounts of epimeric carbinols. This desirable stereoselectivity contrasts vividly with the stereorandom outcome previously found with hydrindenone **5**.[1] tert-Butyl ester **14** (from **13**) was found to be most satisfactory for the three-step double bond transposition sequence (**14**→**15**) that preceded lactone annulation efforts. The previous strategy for lactonization, i.e. S_N' intramolecular attack allylic to the C-8 leaving group by side chain carboxylate was expected to succeed with both epimers of **15**, owing to the mechanistic feasibility of both *syn*- and *anti*- modes of intramolecular displacement[8], and to our own previous experience[1] (**5**→ **6** and **7**).



Reagents: (a) $CH_3CO_2C(CH_3)_3$, LDA, HMPA, THF, -78 °C, 1 h. (b) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, -60 to 25 °C. (c) $NaOCH_3$, CH_3OH, THF, 0 °C, 30 min. (d) DIBAL-H, toluene, -78 °C, (~1:1 mixture **15a** : **15b**).

Initially, lactonization of **15b**[9] was attempted without prior base-induced ester hydrolysis (since the latter was expected to be slow under mild conditions, which were required in order to avoid retroaldol loss of tert-butyl acetate). C-8β Hydroxyl activation (MsCl, Et_3N in THF) led *via* an 1,4-elimination to a cyclopentadiene (**16**: λ_{max}(hexane) 259 nm, ε ~ 10,000; ^{1}H-NMR: vinyl Hs at δ 6.12 & 5.79 ppm, $J_{1,4}$= 2.4 Hz) instead of **6**.

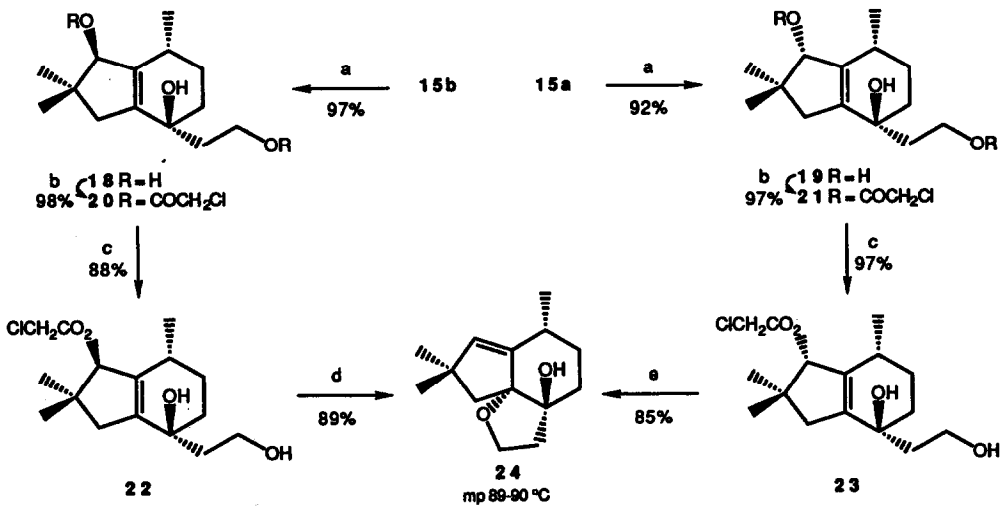
Accordingly, **15b** was carefully hydrolyzed and the dried carboxylate salt (azeotropic removal of water with benzene) subjected to mesylation (as shown below). In this case, a ~1:1 mixture of γ-lactone **6** (^{1}H-NMR: vinyl singlet at δ 5.68 ppm; IR: $\nu_{C=O}$ 1770 cm^{-1}) and diene **17**[10] (^{1}H-NMR: vinyl Hs at δ 4.77 & 4.74 ppm; IR: no $\nu_{C=O}$) was obtained. The latter product resulted from tertiary hydroxyl activation[11], a problem not encountered in



16 **15b** **17**

Reagents: (a) K_2CO_3, H_2O, CH_3OH, 25 °C, 15 days. (b) MsCl, Et_3N, THF, -10 to 25 °C, 12 h.

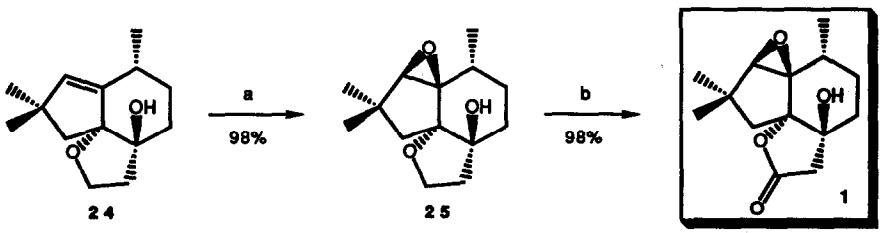
our previous "one-pot" annulation! While the formation of γ-lactone **6**, free of epimer **7**, was a step forward, the unavoidable co-occurrence of decarboxylation product **17** required further modification of the annulation. We rationalized that by increasing the nucleophilicity of the C-4 side chain one could use a "poorer" C-8 leaving group that would be less prone to undergo 1,4-elimination (to a cyclopentadiene) prior to annulation.



Reagents: (a) $LiAlH_4$, Et_2O, 23 °C, 3 h. (b) $(ClCH_2CO)_2O$, cat. DMAP, pyridine, CH_2Cl_2, -78 to 25 °C, 0.5 h. (c) KOH, H_2O, THF, 0 °C, 15 min. (d) i. LDA, THF, HMPA, -78 °C, 2 h; ii. 25 °C, ~ 42 h. (e) $EtN(i\text{-}Pr)_2$, $MgSO_4$, 110 °C, toluene, 24 h.

Thus, both esters **15a** and **15b** were individually reduced ($LiAlH_4$) with intention of cyclizing the resultant β-hydroxyethyl side chains to cyclic ethers. This would be followed by eventual back oxidation (RuO_4) of the tetrahydrofuran ring to a γ-lactone. Triols **18** and **19** were prepared from esters **15b** and **15a**, respectively, and immediately subjected to two-fold acylation with chloroacetic anhydride (first at the primary site, then at C-8). This first-formed bis-chloroacetate (**20** or **21**) in each case was selectively hydrolyzed, leaving the desired monoester-diols **22** and **23** as candidates for intramolecular S_N' alkoxide displacements. Both epimers cyclized satisfactorily to **24**, although under different conditions. Closure of **22** required prior deprotonation of the β-hydroxyethyl side-chain with LDA whereas the **23**→**24** transformation, via preferred *syn* stereochemistry,[12] occurred readily in hot toluene (with Hunig's base present only to quench chloroacetic

acid). Ether **24** (^{1}H-NMR: vinyl singlet at δ 5.50 ppm) was cleanly oxidized with buffered m-CPBA and the resulting epoxide **25** (^{1}H-NMR: epoxide singlet at δ 3.15 ppm) subjected to RuO_4 oxidation[13], providing a 98% yield of 12-noralliacolide (**1**). This sample was identical (^{1}H-NMR, IR, mp and R_f)with material previously synthesized by us[1] and further converted to alliacol A (**2**) and alliacolide (**3**).

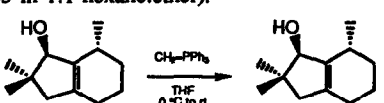


Reagents: (a) m-CPBA, $NaHCO_3$, CH_2Cl_2, -78 to 25 °C, 3.5 h. (b) $RuCl_3 \cdot n\,H_2O$, $NaIO_4$, $NaHCO_3$, CH_3CN, H_2O, CCl_4.

In conclusion, a selective, high-yielding route to the majority of alliacane sesquiterpene lactones[1,2] is now available for the first time. Efforts are underway to extend the utility of advanced intermediates towards additional metabolites of *Marasimus Alliaceus* such as alliacol B.[2]

REFERENCES AND NOTES:

1. Lansbury, P. T.; Zhi, B.-Z. *Tetrahedron Lett.* **1988**, *29*, 5735-5738; Zhi, B.-Z. *The Total Synthesis of 12-Noralliacolide, Alliacol-A and Alliacolide.* The State University of New York at Buffalo 1988.
2. Farrell, I. W.; Halsall, T. G.; Thaller, V.; Bradshaw, A. P. W.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1.* **1981**, 1790-1793; King, T. J.; Farrell, I. W.; Halsall, T. G.; Thaller, V. *J. Chem. Soc., Chem. Comm.* **1977**, 727-728; Avent, A. G.; Hanson, J. R.; Hitchcock, P. B.; Yeoh, B. L. *J. Chem. Soc., Perkin Trans. 1.* **1985**, 2749-2751; Anke, T.; Watson, W. H.; Giannetti, B. M.; Steglich, W. *J. Antibiotics* **1981**, *34*, 1271-1275.
3. Lansbury, P. T.; Zhi, B.-Z. *Tetrahedron Lett.* **1988**, *29*, 179-180.
4. Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413-4416; Ladlow, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1.* **1988**, 1107-1118.
5. Raphael, R. A.; Telfer, S. J. *Tetrahedron Lett.* **1985**, *26*, 489-492.
6. This compound was prepared in 6 steps by B. Zhi (see ref. 1) and optimized to 5 steps (overall yield of 73% from 2-cyclopenten-1-one) by J. J. La Clair (*The First Stereoselective Total Synthesis of the Alliacane Family of Natural Products: Alliacolide, Alliacol A, and 12-Noralliacolide*, The State University of New York at Buffalo 1993). A single crystal X-ray crystal analysis of (±)-**4a** was preformed by Dr. K. Hoogsteen (Merck) and corroborated the relative configuration as depicted. Details will be provided in the full paper.
7. All new compounds were thoroughly characterized by an appropriate combination of ^{1}H- and ^{13}C- NMR (at 400 MHz and 75 mHz, respectively), IR and MS; molecular formulas were established by elemental analysis or high resolution MS determination of exact masses.
8. Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383-7423.
9. Substrate **15b** was tentatively assigned the β-OH configuration based on its increased polarity (as indicated by TLC; R_f (**15b**) = 0.11, R_f (**15a**) = 0.35 in 1:1 hexane:ether).
10. Diene **17** was also produced by the addition of triphenylphosphonium methylide to enone **26**. The isolated product exhibited ^{1}H-, ^{13}C- NMR, IR, and R_f identical with **17** from **15b**.



11. Activation of this site may have originated from the intramolecular mesylation of the C-4 center by a carboxylic-sulfonic anhydride, which in turn was generated by the addition of the carboxylate to "sulfene", followed by an intramolecular proton transfer (from the C-4 hydroxyl to an incipient carbanion).
12. Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073-1074; Huffman, J. W.; Desai, R. C. *J. Org. Chem.* **1982**, *47*, 3254-3258.
13. Kanazawa, A. M.; Correa, A.; Denis, J.-N.; Luche, M.-J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255-256.

(Received in USA 6 May 1993)