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Rearrangement strategies in natural products synthesis

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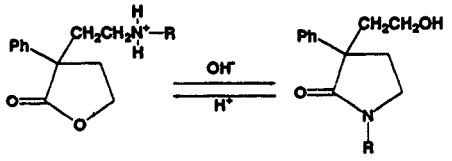
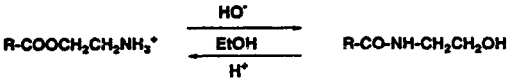
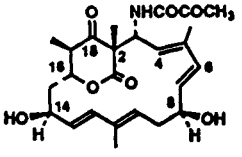
Abstract: Rearrangement reactions are both expected and unexpected elements of natural products synthesis. We describe an unexpected molecular rearrangement first encountered during a recent alkaloid synthesis. We also report the exploitation of the pH-dependent equilibrium between hydroxy-lactams and the isomeric amino-lactones as a key strategic element in some recent total syntheses from our laboratories.

The phenomenon of intramolecular N → O acyl migration has been recognized since the early 20th century as one of the more general rearrangements of the amide bond. In some, but not all systems, this rearrangement is a pH-dependent equilibrium. Two characteristic examples are illustrated below (ref. 1).



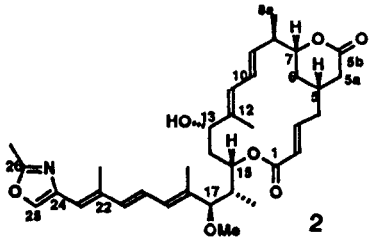


Over the last decade our group has targeted several natural product syntheses in which such amide rearrangements are a central element of strategic design. Such targets include the macrolide antibiotic Lankacidin C (**1**), the antitumor agent didesepoxyrhizoxin (**2**), and the rare acaricidal and antitumor alkaloid altemicidin (**3**).



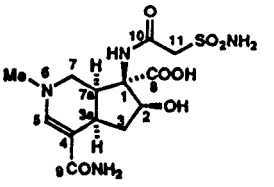
1

Lankacidin C



2

Didesepoxyrhizoxin

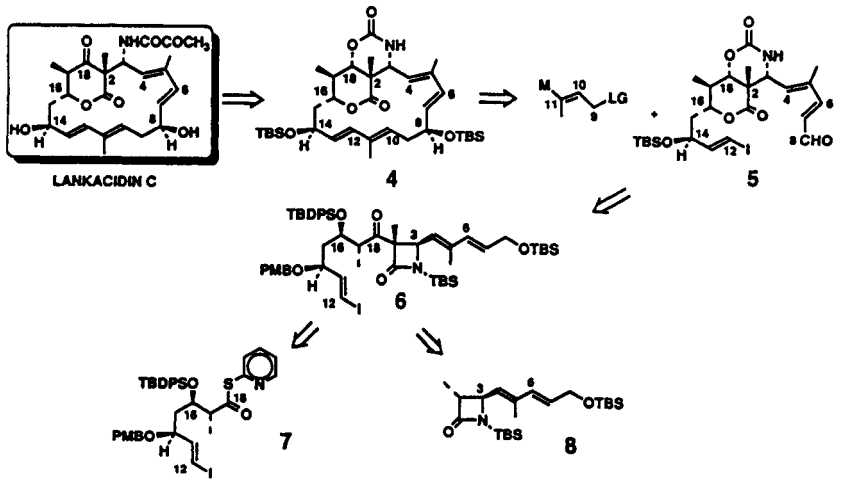


3

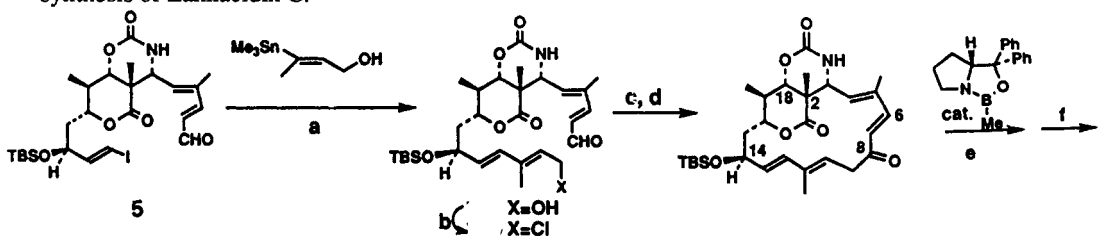
Altemicidin

Enantioselective Synthesis of Lankacidin C

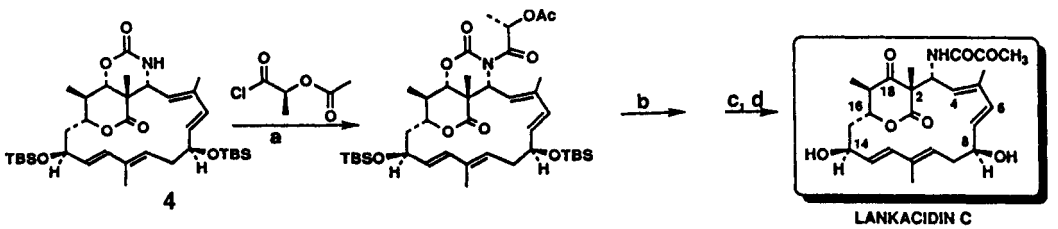
The 1,3-dicarbonyl system within the pyrandione ring of **1** confers upon Lankacidin C extraordinary lability toward mild base or mild acid. It was therefore deemed essential to approach this target by working toward the C(18)-reduced tricyclic carbamate **4** as the proximate precursor. Our strategy to Lankacidin C is summarized in the retrosynthetic analysis below. Carbamate **4** would be constructed by cyclization of the seco iodo-aldehyde **5** employing a 4-carbon linch-pin synthon, in which C(9) and C(11) bear a leaving group ("LG") and a metal (M"), respectively. The requisite iodo-aldehyde **5** would be generated by intramolecular acyl-migration of the C(18)-reduced β-lactam carbonyl (derived from **6**) from N to C(16)-O.



As detailed in our recent full paper, this amide rearrangement strategy was successfully completed (ref. 2). In a highly convergent sequence, the enolate of β-lactam **8** (from L-aspartic acid) was condensed with thiopyridyl ester **7** (from D-arabinose) to give acyl-lactam **6**. K-Selectride reduction of **6** at C(18) gave the α-carbinol which upon desilylation, acid-catalyzed rearrangement and subsequent conventional elaboration gave the enantiopure iodo-aldehyde **5**. Stille coupling of **5** with *E*-3-trimethylstannyl-2-buten-1-ol generated stereospecifically the C(11)-C(12) bond. Aldehyde umpolung via a Stork-Takahashi closure (ref. 3) led to the tricyclic ketone. Stereoselective Corey oxazoborole reduction of the C(8)-carbonyl and subsequent dissection of the carbamate unit led as shown to the first, enantioselective total synthesis of Lankacidin C.



a) cat. $PdCl_2(CH_3CN)_2$, DMF, rt, 90 %. b) 2,6-Lutidine, LiCl, MsCl, DMF, 0°C. c) cat. KCN/18-Crown-6, TMSCN. d) LiHMDS, THF, -78°C; AcOH, THF-H_2O, rt, 20h; 1% aq. NaOH, 61% from 15a. e) oxazaborole catalyst, BH_3-THF, THF, -10°C, 89%. f) TBSCl, Imidazole, DMF, rt, 95%.

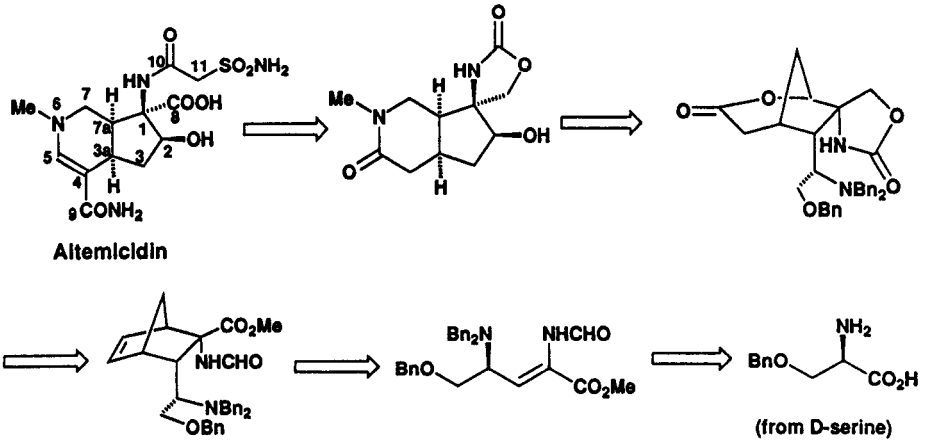


a) LiHMDS, THF, -78°C, 85%. b) LiOH, THF-H_2O (3:1), 0°C, 82%. c) Dess-Martin periodinane, CH_2Cl_2, rt, 96%. d) HCOOH-THF-H_2O (3:6:1), rt, 3h, 82%.

Thermal Rearrangement of an α-Formamidoacrylate Dienophile

Instead of lactam to lactone rearrangement as shown above, our approach to altemicidin (presented in retrosynthetic summary) will feature a critical lactone to lactam rearrangement to generate the core bicyclic system of the target. The bridged lactone intermediate would arise by oxidative transformation of the bicycloheptene pictured. This bicycloheptene would be prepared by stereospecific Diels-Alder addition of the unsaturated α-formamido ester shown (from D-serine) to cyclopentadiene.

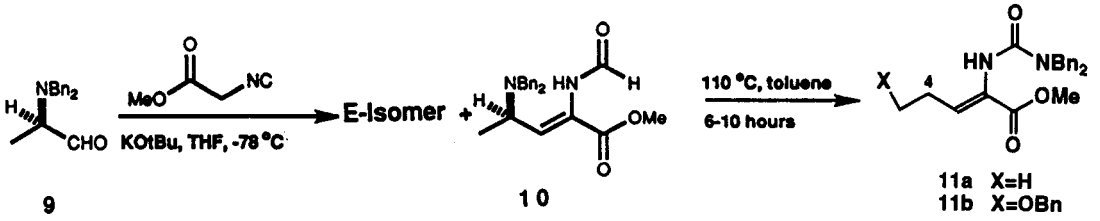
RETROSYNTHETIC STRATEGY



Altemicidin

(from D-serine)

Schöllkopf condensation (ref. 4) of MeO_2CCH_2NC with *R*-aldehyde **9** gave 46% of the desired Z-enoate **10**, mp 110 °C and 23% of the oily E-enoate. In a study of the thermal stability of each isomer, we observed that heating **10** for several hours in refluxing toluene, *t*-BuOH or *n*-PrOH converted it in good yield to an unknown isomer, whereas the E-enoate gradually decomposed. The structure of the isomer was shown by X-ray to be the urea **11a**! In the serine series, the analogous thermal isomerization to **11b** was observed.

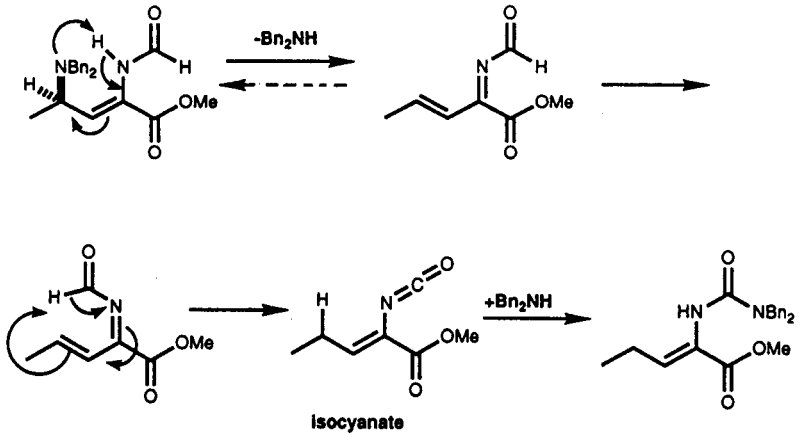


9 **10**

11a X=H
11b X=OBn

Crossover experiments (ref. 5) established that this thermal rearrangement was intermolecular, in the sense that the dibenzylamino group leaves, then readds, to the carbon framework of the substrate **10**. Deuterium labeling at the formyl group (e.g., **10**-NHCDO) led to much lower yield of the C(4)-deuterated variant of **11a**. From these and other data, including a control experiment showing that when 1-naphthylisocyanate is added to a .0001 M solution of i-Pr_2NH in CH_3OH only the urea is formed (to the exclusion of the carbamate), the following elimination-addition mechanism was proposed.

An Elimination-Addition Mechanism

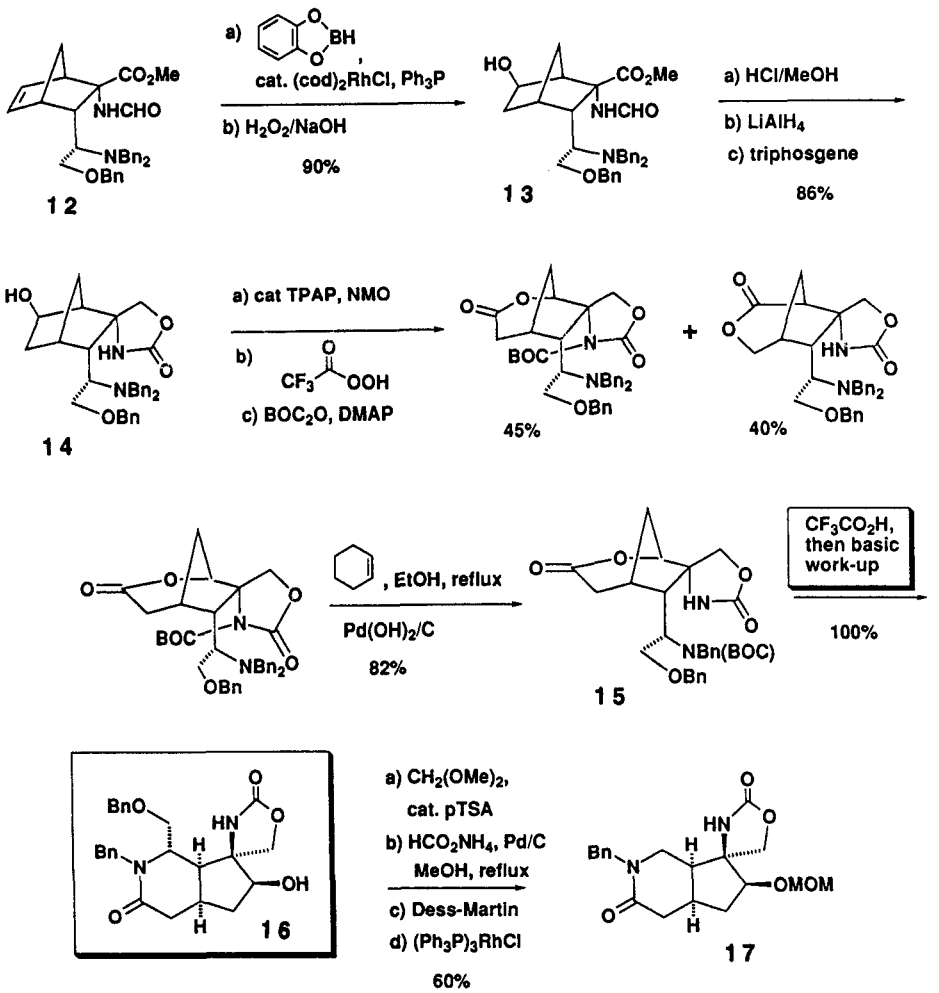


Isocyanate

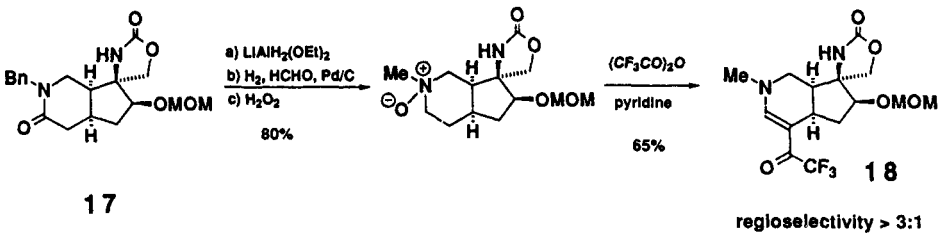
The obligatory role of an isocyanate was ultimately confirmed by cooling a reaction carried to ca. 20% completion. A strong IR maximum at 2220 cm^{-1} was easily discerned, and quenching of this cooled reaction with *i*-Pr_2NH led to the isolation of the N,N-diisopropyl analog of **11a**, arising from trapping of the isocyanate intermediate by the added *i*-Pr_2NH.

Enantioselective Total Synthesis of (–)-Altemicidin

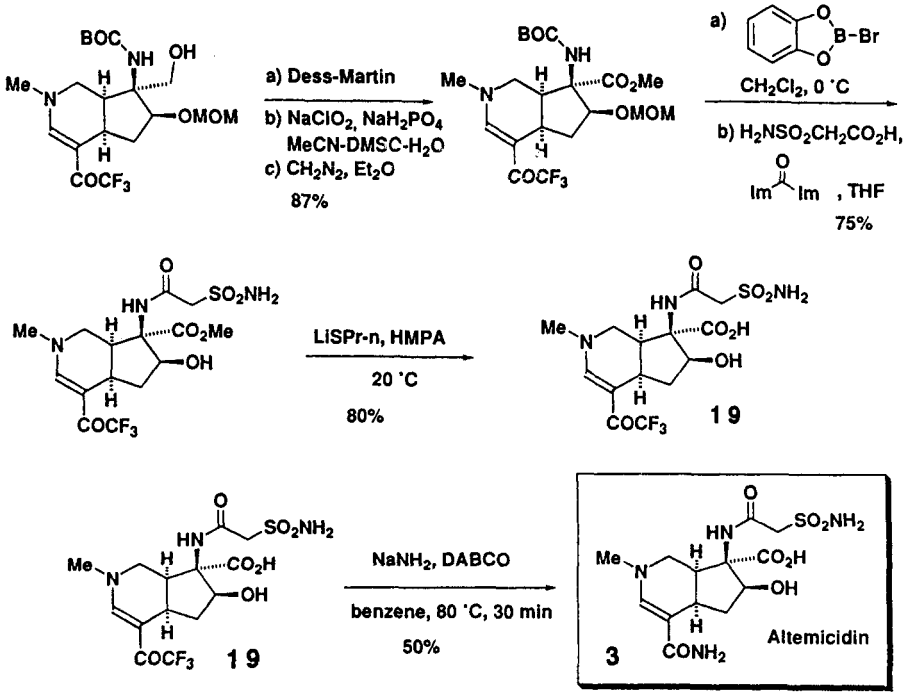
Fortunately, the Diels-Alder step of our altemicidin synthesis could be carried out at 0 °C employing 2+ equiv. of Et_2AlCl, as noted by Reetz (ref. 6). This produced in 87% yield the crystalline bicycloheptene **12**. Regio- and stereoselective rhodium-mediated catecholborane addition, then oxidation, converted **12** to the exo-carbinol **13** in 90% yield (ref. 7). Oxidation of carbinol **13** gave the ketone, but Baeyer-Villiger rearrangement to the desired lactone gave largely the incorrect regiochemistry. After very extensive studies, we obtained optimum results by proceeding via the cyclic carbamate **14**, which on oxidation by TPAP-NMO, then CF_3CO_3H, led on BOC_2O/DMAP work up to 45% of the BOC-protected desired ketone and 40% of the unprotected wrong regioisomer. Selective transfer-hydrogenation removed one N-Bn group, followed immediately by BOC-transfer to yield **15**. To our delight, CF_3CO_2H removal of the BOC group followed by addition of base to pH > 11 led *in quantitative yield* to the transannular acyl migration product, the lactam **16**. Removal of the pendant CH_2OBn chiral auxiliary by Rh-mediated decarbonylation gave the bicyclic altemicidin precursor, N-benzylpiperidone **17**.



Conversion of the simple N-benzylpiperidone **17** into the vinylogous urea substructure of altemicidin posed as a formidable challenge. After several false starts, we found that reductive deoxygenation of the lactam, followed by *in situ* catalytic debenzylation and N-methylation in the presence of HCHO, gave an N-methylpiperidine. This was converted by H_2O_2 to the N-oxide, which underwent Potier-Polonovski rearrangement and trapping of the enamine by $(CF_3CO)_2O$ to give the trifluoromethyl vinylogous amide **18** (ref. 8). The favorable regiospecificity of the latter rearrangement in this instance was noteworthy.



The carbamate ring was transformed by conventional chemistry to the sulfonamide acid **19** of the natural product. At this point, the final conversion of $COCF_3$ in **19** to $CONH_2$ was tackled. Although we found on models that $CH_3Al(Cl)NH_2$ (Weinreb's reagent), followed by *t*-BuOK, converts such $COCF_3$ groups cleanly to C≡N with loss of CF_3^- (ref. 9), this could not be usefully exploited here. Ultimately, we were able to carry out the required conversion of **19** employing the DABCO-mediated version of the Haller-Bauer reaction (ref. 10).



We have thus completed the first total synthesis of (–)–altemicidin (ref. 11) by an enantioselective route employing a lactone to lactam amide rearrangement, in which a bicycloheptane-derived lactone is converted quantitatively to an azaindane system. Viewed with the lactam to lactone rearrangement used in Lankacidin synthesis, and the amide to urea thermal rearrangement of the Reetz dienophiles, we conclude that judicious use of intramolecular amide rearrangements remains a powerful option in the design of appropriate synthesis strategies (ref. 12).

Acknowledgements. We gratefully acknowledge the skill and dedication of members of the Rochester team who made this work possible: B. Blass, K. M. J. Brands, G. Dorey, I. Kaldor, K. Koch, and K. Liu.

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