Tetrahedron Letters, Vol. 33, No. 19, pp. 2641-2644, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

2-PHENYLOXAZOLINES AS CARBOXYLATE PRECURSORS - APPLICATION TO THE SYNTHESIS OF ASYMMETRIC BRANCHED-CHAIN STRUCTURES

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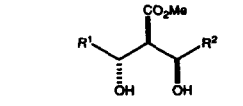
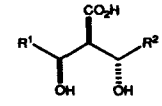
SUMMARY: A synthetic approach to the title compounds is presented that features the asymmetric elaboration of a chiral, non-racemic oxazoline followed by a two-step oxidative ring cleavage of the heterocycle to a triamide for further transformation.

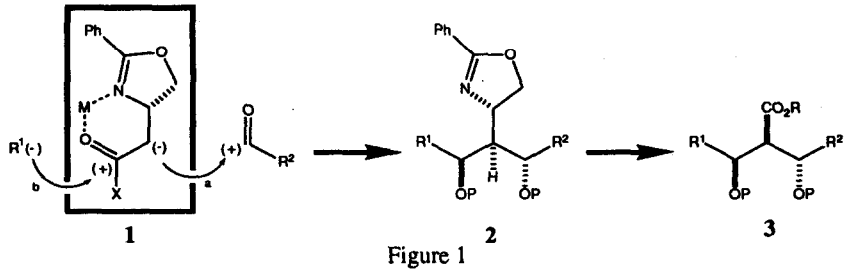
Branched, acyclic arrays are frequently encountered in macrocyclic, polyoxygenated natural products. For example, both the ansamycins and the polyene macrolide antibiotics include members whose structures incorporate the branched *syn/anti* subunits indicated, though enantiomerically related to each other.[1,2] On-going synthetic objectives in our laboratories led us to study the application of a versatile synthetic intermediate derived from L-aspartic acid (**1**, X=^{t}BuS, figure 1) to this problem with the result that a practical strategy has been developed for the assembly of this framework which features an efficient conversion of asymmetric 2-phenyloxazolines to carboxylic acid derivatives.[3]



Ansamycins
(*i.e.*, C23-C25 of Streptovaricin C)



Polyene Macrolide Antibiotics
(*i.e.*, C15-C17 of amphotericin B)



1 **2** **3**

Figure 1

This approach is illustrated in figure 1 and relies upon an aldol reaction of an asymmetric, chelated enolate (via arrow a, X=^{t}BuS in **1**) followed by chelation-controlled alkylation of the subsequently derived aldehyde (via arrow b, X=H on adduct **1**)[4] to afford compounds **2** in high overall yields and diastereoselectivities.[5] Conversion of the asymmetric oxazolines to the desired carboxylate derivative **3** was envisioned using Wasserman's singlet oxygen oxidation of oxazoles to triamides (figure 2)[8] which, in turn, requires a preliminary oxidation of the 2-phenyloxazolines to the requisite oxazoles.[9] We were gratified to observe that these 2-phenyl-5-substituted oxazolines **2** were oxidized to the desired oxazoles **4** in exceedingly efficient fashion using 1-2 equivalents of 2,3-dichloro-5,6-dicyanoquinone (DDQ) in refluxing benzene for 30-60 minutes (Table I).[10] As illustrated by the transformations **4c**→**4g** and **4f**→**4h**, these oxazoles are useful synthetic intermediates for subsequent transformations that may prove problematic on the oxazoline substrates.[11]

Wasserman oxidation of oxazoles

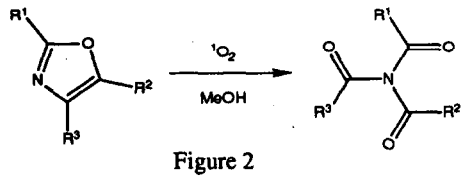
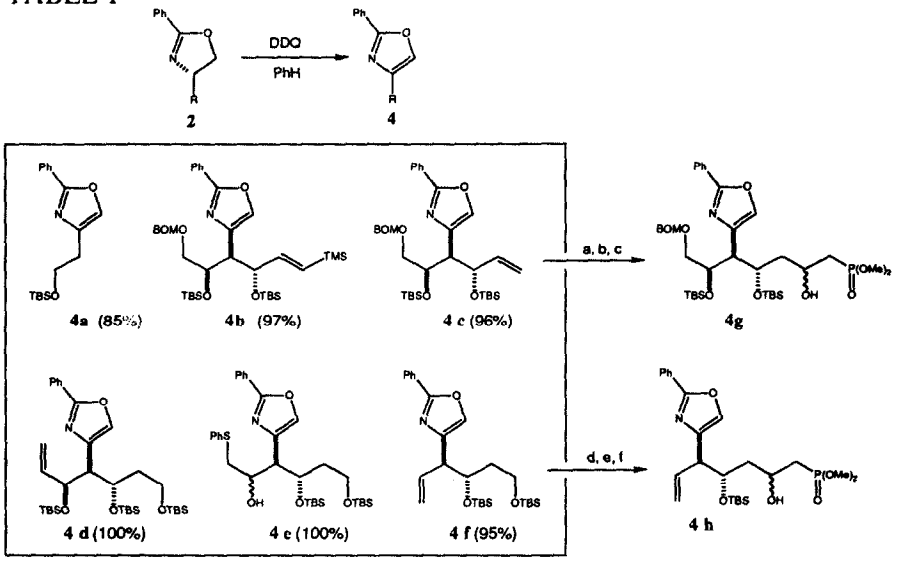


Figure 2

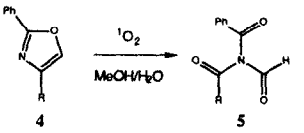
TABLE I

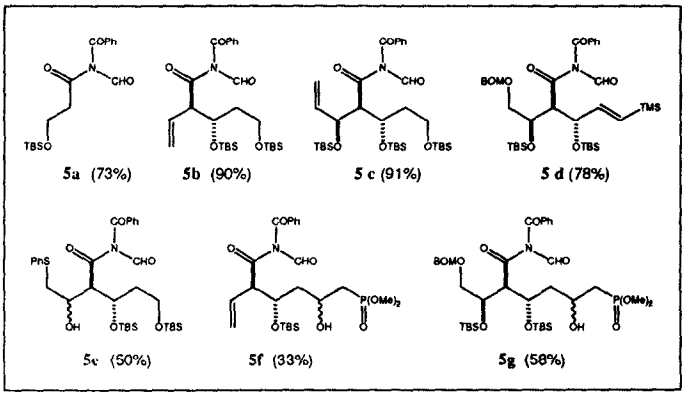


Reagents: (a) BH_3•DMS, CH_2Cl_2; NaO_2H (53%); (b) $(COCl)_2$, DMSO, Et_3N (90%); (c) $(MeO)_2P(O)CH_2Li$, THF (92%); (d) pyridine•HF, pyridine (90%); (e) Dess-Martin oxidation (98%); (f) $(MeO)_2P(O)CH_2Li$, THF (80%)

With efficient access to the required oxazoles, Wasserman oxidation of the heterocycle to the triamide was examined. As shown in Table II, this oxidation proceeded in modest to excellent yields. It was found that using MeOH or MeOH:H_2O (1:1) as the solvent effectively suppressed competing ene reactions with the double bond in those substrates containing an olefin (see **5b**, **5c**, **5d**, and **5f**).[12] As indicated, the yields for triamide formation were high when fully protected substrates were employed, while those substrates containing unprotected alcohols afforded these products in significantly lower yields. These depressed yields may result from interception by this unprotected or reactive functionality of metastable intermediates (such as the endoperoxide that results from the initial $^1O_2$ cycloaddition) formed in the course of triamide formation.[13]

TABLE II





The last stage of the strategy to the targeted asymmetric arrays requires cleavage of the triamide to the desired carboxylic acid derivative. This necessitates cleavage of the acyl nitrogen bond bearing the R^3 substituent in figure 2. Both intermolecular and intramolecular

approaches were examined for this purpose (figure 3). In the former approach, it was found that treatment with aqueous base resulted in exclusive cleavage of the undesirable bonds to yield the amide **6** from triamide **5c**. Fortunately, the amide could be quantitatively converted to its methyl ester with methanol and an acidic resin.[14] However, these rather strong reaction conditions also removed the silyl protecting groups, requiring an additional step for reprotection to give the desired compound **7**. While the chemical efficiency of this sequence is extremely high for this substrate, it was desirable to find a means to effect the cleavage reaction without resorting to deprotection/reprotection, especially as more complex substrates are contemplated for future application of this strategy. With this in mind, it was hoped that intramolecular cleavage of the triamide could be realized to afford the product as a lactone. It was gratifying to find that, in a single step, the primary alcohol in triamide **5b** could be selectively deprotected and cyclized to afford the desired product **8** in high yield using pyridine•HF in pyridine. In this way, lactone **8** could be efficiently obtained from the corresponding oxazoline in three chemical operations and 73% overall yield.

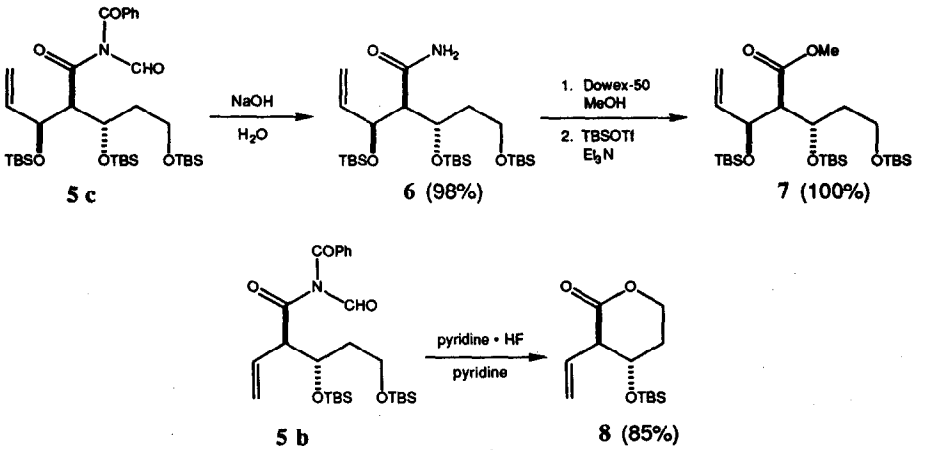


Figure 3

In summary, an effective strategy has been developed to branched chain asymmetric arrays that exploits chiral, non-racemic oxazolines as both the source of chirality and the desired carboxylic functionality. The two-stage oxidation/cleavage sequence used to process the oxazolines often proceeds in a very efficient manner and accommodates considerable functionality. With these results, we have extended the synthetic utility of asymmetric oxazolines by demonstrating their equivalency with carboxylic acid functionality, complementing their previously demonstrated equivalency with aldehydes[3a-c] and epoxides.[3d] Application of this strategy to the synthesis of complex, highly oxygenated compounds will be the subject of future reports.

ACKNOWLEDGEMENT: The financial support of the National Institutes of Health (AI 17959) is gratefully acknowledged.

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4. For the preparation of the aldehydes used in subsequent alkylations: (i) $LiNEt_2$, THF, -78°C; (ii) RCHO, -78°C; (iii) $^tBuMe_2SiOTf$, Et_3N, CH_2Cl_2, -78°C; (iv) DIBAL, CH_2Cl_2, -78°C. Overall yields (diastereoselectivities) for RCHO: H_2C=CHCHO, 91% (>98%); Me_3SiCH=CHCHO, 85% (94%); $^tBuMe_2SiOCH_2CH_2CHO$ 90% (84%). For the preparation of compound **1**, where X=H, see reference 3c.

5. For conversion of the aldehydes prepared as described in reference 4 to compounds **2** (Table I): Compound **2b** - (i) $(BnOCH_2OCH_2)_2CuLi$,[6] THF, -78°C; (ii) $^tBuMe_2SiOTf$, Et_3N, CH_2Cl_2, 0°C (95% yield, >98% diastereoselectivity); Compound **2c** - same as for compound **2b** (66% yield, 93% diastereoselectivity); Compound **2d** - (i) vinylmagnesium bromide, THF, -78°C, (ii) $^tBuMe_2SiOTf$, Et_3N, CH_2Cl_2, -15°C (58% yield, >98% diastereoselectivity); Compound **2e** - $PhCH_2Li$, THF, -78°C (40% yield, no selectivity); Compound **2f** - CH_2Br_2, $TiCl_4$, Zn°, THF-CH_2Cl_2, room temp (65% yield)[7]. Compound **2a** was prepared in 90% overall yield via: (i) $NaBH_4$, EtOH, 0°C; (ii) $^tBuMe_2SiOTf$, Et_3N, CH_2Cl_2, 0°C.

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11. For example, hydroboration of **4c** proved to be exceedingly difficult as conditions required to effect the addition of BH_3 to the double bond also resulted in decomposition of the oxazoline ring.

12. When the more typically employed solvents were used (such as $CHCl_3$ or EtOAc), the ene-type products could be obtained as the major component of the reaction mixtures - up to 8:1 in favor of the undesired material over the desired oxazole oxidation. For a review of the sensitized photooxygenation of olefins see: Denny, R.W.; Nickon, A. *Org. React.* **1973**, *20*, 133.

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(Received in USA 11 November 1991; accepted 20 February 1992)