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STEREOSELECTIVE SYNTHESIS OF 1,2,3-TRISUBSTITUTED CYCLOPROPANES AS NOVEL DIPEPTIDE ISOSTERES

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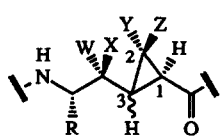
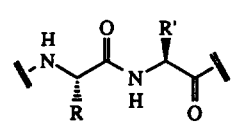
Summary. The design and stereoselective synthesis of a novel peptide structural replacement containing a 1,2,3-trisubstituted cyclopropane is described.

Linear oligopeptides that adopt well defined three dimensional structures upon binding to their receptors or enzyme binding (active) sites are typically conformationally flexible in solution. We have been engaged in a general program directed toward the design and stereoselective synthesis of rigid structures that mimic selected features of oligopeptide secondary structure upon substitution for a peptide segment.[1] Such peptide mimics not only enforce specific spatial orientations upon the substituents and functionality on the resulting framework, but the resulting pseudopeptide is also resistant to degradation by proteinases. Consequently, the invention of novel peptide replacements has recently assumed tremendous importance as a tactical device for the rational design of ligands for biological receptors, and numerous advances in this area of molecular recognition have been recorded.[2]

Some time ago, it occurred to us that 1,2,3-trisubstituted cyclopropanes related to **1** might constitute useful surrogates for the natural dipeptide unit **2**. A number of structural considerations lead to this invention which is conceptually different from the known class of 1-aminocyclopropane carboxylic acids.[3] Firstly, insertion of a cyclopropane in the peptide backbone would confer increased rigidity upon the matrix. The amino acid side chains Y and Z, which are known to play crucial roles in recognition and transduction, could be specifically oriented relative to the peptide backbone by manipulation of the cyclopropane stereochemistry at C(2) of **1**; this feature may be exploited to achieve optimal interaction with the receptor. Additionally, D- or L-amino acid residues may be mimicked by controlling absolute stereochemistry at C(1) (*C*-terminal region) of the cyclopropane ring. The ability to enforce an extended conformation (β-strand) or induce a turn would be controlled by the stereochemistry at C(3), which bears the *N*-terminal peptide region. Directional hydrogen bonding capabilities may be controlled and maintained by varying the nature of W and X. Finally, replacement of the amide bond removes a potential site for enzymatic hydrolysis. Molecular modeling studies employing X-ray data of selected aspartate proteinase/inhibitor complexes[4]



1: W, X = H, OH, O
Y, Z = H, alkyl, aryl



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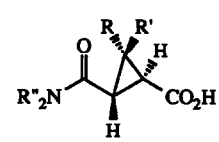
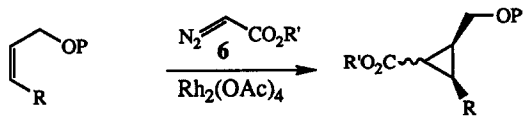


3: R = R" = alkyl, aryl; R' = H
4: R = H; R' = R" = alkyl, aryl

suggested to us that cyclopropanes of the general structures **3** and **4** would be intriguing targets to serve as the first members of this novel class of cyclopropane-derived dipeptide replacements **1**. We envisioned that incorporation of such surrogates in new inhibitor-derived pseudopeptides would conformationally restrain a segment of the backbone in an extended conformation, thereby enhancing binding. We now describe an efficient protocol for stereoselective synthesis of 1,2,3-trisubstituted cyclopropanes **3** that may be easily modified for the production of diastereomer **4**.

In the first approach directed toward the stereoselective synthesis of trisubstituted cyclopropanes, we explored the efficacy of rhodium-catalyzed cyclopropanation of protected *Z*-allylic alcohols **5**.[5] Since allylic alcohol derivatives are known to react with carbenoids to form ylids that undergo [2,3]-sigmatropic rearrangements,[6] the allylic alcohols were protected as *tert*-butyldimethylsilyl or trityl ethers[7] to sterically obviate such processes. Toward the goal of enhancing the stereoselectivity of the cyclopropanation step, *Z*-allylic alcohols were employed, and the use of bulky diazoesters **6** was explored.[8] However, despite a variety of attempts that are summarized in Scheme 1, we were unable to achieve significant levels of stereochemical control in the cyclopropanation, and mixtures (ca 2:1) of **7** and **8** were invariably obtained.

SCHEME 1



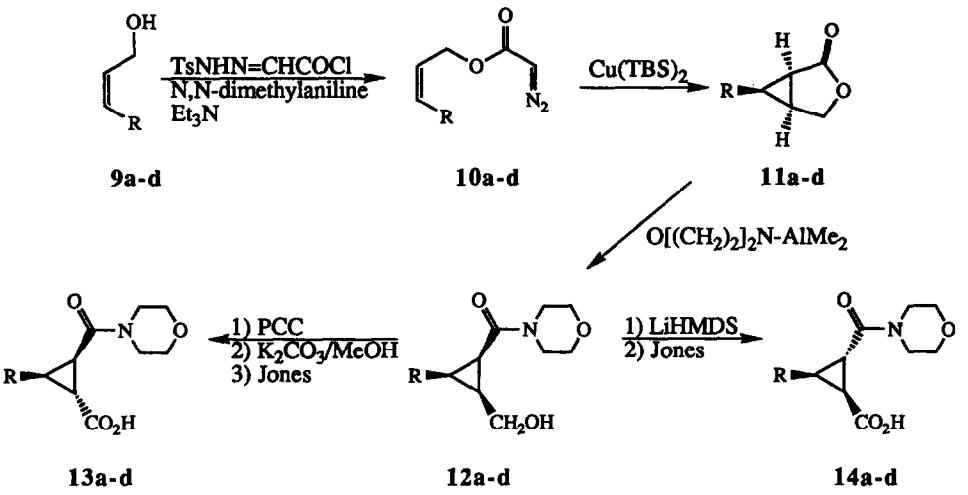
5 **7**: α-CO_2R' **8**: β-CO_2R'

P = *tert*-butyldimethylsilyl, trityl
R = alkyl, aryl
R' = ethyl, 2,3,4-trimethyl-3-pentyl

Since bimolecular cyclopropanations could not be applied to the problem at hand, we reasoned that the intramolecular cyclopropanation of representative allyl diazoacetic esters **10a-d**[9] might constitute the basis of a useful solution (Scheme 2). Owing to geometric constraints, cyclizations of **10a-d**, which were readily available from the corresponding alcohols **9a-d**, necessarily delivered cyclopropanes **11a-d** in which all three substituents were cis. Tactics to achieve the selective epimerization of one of the functionalized substituents on the cyclopropane were devised to allow access to the targets **13a-d** and **14a-d**. Some of the details of these efforts are recorded below.

The requisite *Z*-allylic alcohols **9a-d**[10] were transformed to the corresponding diazoacetic esters **10a-d** [(a) TsNHN=CHCOCl[11] (1.3 equiv); *N,N*-dimethylaniline (1.25 equiv); CH_2Cl_2; 0 °C; 10 min. (b) Et_3N (5.3 equiv); 0 °C (15 min) → RT (30 min); (83 - 93%)].[12,13] The unsaturated diazo esters **10a-d** underwent smooth cyclopropanation to give lactones **11a-d** upon slow addition to a refluxing solution of bis-(N-*tert*-butyl-salicyladiminato)copper (II)[14] catalyst (0.05 equiv) [$PhCH_3$; 111 °C; 16 h; (75 - 90%)]. The lactones **11a-d** were converted into the corresponding morpholine amides **12a-d** [$O(CH_2CH_2)NAlMe_2$[15] (3 equiv); CH_2Cl_2; 40 °C; 48 h; (70 - 81%)]. At this juncture, it was possible to prepare either of the diastereomeric carboxy amides **13a-d** or **14a-d**. Thus, oxidation of the primary alcohol function in **12a-d** [PCC[16] (1.5 equiv); CH_2Cl_2; RT; 48 h; (69 - 82%)] afforded intermediate aldehydes that were readily epimerized[17] upon exposure to methanolic potassium carbonate [RT; 18 h; (72 - 88%)]; subsequent Jones oxidation (5.6 equiv) [acetone; 0 °C; 2 h; (84 - 94%)] afforded

SCHEME 2



Series **a**: R = Et
b: R = *i*-Bu
c: R = $CH_2C_6H_{11}$
d: R = Ph

the carboxylic acids **13a-d**. The application of this approach to the preparation of the diastereomeric series **14a-d** is exemplified by epimerization of the amide **12d** [$LiN(SiMe_3)_2$ (3 equiv); THF; RT (30 min)] followed by Jones oxidation as before to give the acid **14d** (70%, 2 steps).

In preliminary investigations we have also examined several modifications of these procedures in efforts to devise an approach to the asymmetric synthesis of cyclopropanes **13a-d** and **14a-d**. For example, when the cyclopropanation of **10b** was catalyzed with the Aratani catalyst,[18] **11b** (absolute stereochemistry unknown) was obtained in greater than 65% enantiomeric excess. Other catalysts are being examined to improve the level of enantioselectivity. We are also exploring several enzymatic processes[19] that might be applied to the resolution of lactones **11a-d** or compounds derived therefrom.

Thus, we have developed a general method for the highly stereoselective synthesis of racemic 1,2,3-trisubstituted cyclopropanes, and there is an excellent prospect for discovering methods for their asymmetric synthesis. Incorporation of cyclopropanes of types **3** and **4** as peptide mimics in the context of designing novel enzyme inhibitors and peptide hormone antagonists will be reported in due course.

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13. The structure assigned to each compound was in full accord with its spectral (^{1}H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of all new compounds were obtained by recrystallization, preparative HPLC, or flash chromatography and gave satisfactory data for elemental composition via combustion analysis and/or high-resolution mass spectrometry. All yields are based on isolated products of >95% purity as judged by ^{1}H NMR.
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