On the halogenation of N(1),N(2)-di-t-Boc-5-hydroxy-piperazic acid esters and the conformational preferences of their 5-halo-piperazic acid products. The importance of A1,3 rotameric-strain in determining N(2)-acyl piperazic acid ring conformation


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On the halogenation of \(N(1),N(2)\)-di-\(t\)-Boc-5-hydroxy-piperazic acid esters and the conformational preferences of their 5-halo-piperazic acid products. The importance of \(A^{1,3}\) rotameric-strain in determining \(N(2)\)-acyl piperazic acid ring conformation

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In this paper, an unambiguous synthetic strategy is reported for the preparation of enantiomerically pure cis-5-halo-piperazic acid derivatives in single diastereoisomer form. Contrary to the recent report by Shin et al. (Ref. 6), in which it is claimed that the Ph\(3P\) and \(N\)-chlorosuccinimide (NCS)-mediated chlorination of (3S,5S)-trans-\(N(1),N(2)\)-di-\(t\)-Boc-5-hydroxy-piperazic acid derivative 1 proceeds with retention of configuration at C(5) to give 2, we now show that this and related Ph\(3P\)-mediated halogenations all occur with \(S_N^2\) inversion at the alcohol center, as is customary for such reactions. Specifically, we demonstrate that the (3S,5R)-trans-5-Cl-piperazic acid derivative 2 claimed by Shin et al. (Ref. 6) is in actual fact the chlorinated (3S,5S)-enantiomer 6, which must have been prepared from the cis-(3S,5S)-alcohol 3, a molecule whose synthesis is not formally described in the Shin paper. We further show here that the cis-(3R,5R)-5-Cl-Piz 13 claimed by Shin et al. in Ref. 6 is also (3S,5R)-trans-5-Cl-Piz 6. Authentic 13 has now been synthesized by us, for the very first time, here. Since Lindsley and Kennedy have recently utilized the now invalid Shin and coworkers’ retentive Ph\(3P\)/NCS chlorination procedure on 1 in their synthetic approach to piperazimycin A (Ref. 10), it follows that their claimed 5-Cl-Piz-containing dipeptide 25 probably has the alternate structure 26, where the 5-Cl-Piz residue has a 3,5-cis-configuration. The aforementioned stereochemical misassignments appear to have come from a mix-up of starting materials by Shin et al. (Ref. 6), and an under-appreciation of the various steric and conformational effects that operate in \(N(2)\)-acylated piperazic acid systems, most especially rotameric \(A^{1,3}\)-strain. The latter has now been unambiguously delineated and defined here under the banner of the \(A^{1,3}\)-rotamer effect.

**Keywords:**
- 5-Halo-Piperazic acids
- Ph\(3P\)/NCS chlorination
- The \(A^{1,3}\)-Rotamer Effect
- Piperazimycin A
- Kutzerides, Monamycins
- Bromomonamycins
- \(N(2)\)-Acyl-Piperazic Acids

Configurational isomers of 5-chloro- and 5-bromo-piperazic acid have been encountered in Nature in many biologically-interesting cyclodepsipeptide natural products. These include the piperazimycins, the kutzerides, the monamycins, and the bromomonamycins to name but a few (Fig 1). In light of this, there has been substantial interest in the chemical synthesis of halogenated piperazic acid derivatives, most especially the enantiopure \(trans\)-5-chloro-piperazic acid (5-Cl-Piz) variants. Our own synthetic effort in this area began in the period 1998-2000, when we first successfully applied our tandem asymmetric electrophilic hydrazination-nucleophilic cyclization technology to stereoselective construction of (3S,5R)- and (3R,5S)-\(trans\)-5-
chloropiperazic acids, as part of our monamycin H1 total synthesis programme.\textsuperscript{3}

More recently the Hale group has worked with the Walsh and Schroeder teams, to synthesize several trans-(3S,5R)-5-Cl-Piz reference standards that have helped provide powerful new insights into the biosynthetic origins of the kutznerides.\textsuperscript{9} Specifically, a thioacyl carrier-bound peptide was identified on the biosynthetic path to the kutznerides that contains a cis-5-Cl-Piz-residue.\textsuperscript{9} This is then epimerized by an, as yet, undetermined mechanism to produce the trans-(3S,5R)-5-Cl-Piz unit found in the natural products themselves.\textsuperscript{9}

As a consequence of these efforts, it was deemed desirable to have synthetic access to a variety of different 3,5-cis-5-Cl-Piz derivatives for further studies in this area and, with this in mind, we were drawn to the 2001 report of Shin and coworkers\textsuperscript{6} in which it was claimed that the (3R,5S)-Piz alcohol 1 could be \textit{retrively} chlorinated with PhP\textsubscript{3} and N-chlorosuccinimide in CH\textsubscript{2}Cl\textsubscript{2}, to obtain the (3R,5S)-5-chloride 2.

If such a transformation was indeed possible (and subsequent work by Lindsey and Kennedy\textsuperscript{7} appeared to suggest that it was), we believed that we might be able to gain rapid access to our desired (3S,5S)-cis-configured chloride 4 from the cis-configured (3S,5S)-alcohol 3, previously prepared by our team,\textsuperscript{2} so obviating the need to develop a completely new synthetic route.

We therefore re-synthesized the known (3S,5S)-alcohol 3 from D-mannitol by our 1998 route\textsuperscript{3} and we examined its chlorination with NCS/PhP\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} at rt and, not too surprisingly in hindsight, we observed that chlorination did not proceed with retention of configuration, \textit{but with clean S\textsubscript{2} inversion}, as is customary for such chlorination reactions (Scheme 1).\textsuperscript{1,2}

Specifically, the process afforded the trans-configured chloride 6 that had previously been synthesized by us\textsuperscript{2} in 61% yield, alongside a small quantity (8%) of the 4,5-cycloalkene 5.\textsuperscript{5} The latter arose from an \textit{anti}-E2 elimination of the axial H4 and O-chlorophosphorane groups in the \textit{C\textsubscript{3}} chair conformation, where the C(3)-carboxymethyl is axial.

Despite the fact that the \textsuperscript{1}H NMR spectrum of chloride 6 was rather poorly resolved at 400 MHz in CDCl\textsubscript{3}, due to the existence of urethane rotamers, the two signals for H4 were relatively sharp and allowed extraction of key coupling constants (see the Supporting Information, SI). Specifically, there was a large apparent td for the H4ax resonance at \textit{\delta} 1.81, which allowed the following \textit{J} values to be determined: \textit{J}H4eq,H4ax = 5.9 Hz, \textit{J}H4ax,H5ax = 12.9 Hz and \textit{J}H4ax,H4eq = -12.9 Hz. Likewise, in \textit{d}-DMSO, the H4ax resonance appeared at \textit{\delta} 1.85 as a well resolved ddd with vicinal coupling constants \textit{J}H4ax,H5ax = 11.6 Hz and \textit{J}H4eq,H4ax = 6.0 Hz. The magnitudes of these various coupling constants were all consistent with H-4ax and H5 being antiplanelar, and H3 sitting equatorially within a \textit{C\textsubscript{3}} chair conformation that placed the C(3)-carboxymethyl axial and the C(5)-Cl equatorial.

![Scheme 1. PhP\textsubscript{3}-mediated chlorinations of 3.](image)

So why should this particular chair conformation be so readily adopted by 6 when the \textit{A}-value for a carbomethoxy group (1.27) is so much larger than that of a chloride (0.43)?\textsuperscript{10} The answer lies in the significant rotameric allylic A\textsubscript{1,3}-strain that arises between the bulky N(2)-BO\textsubscript{u}-s substituent and the vicinal C(3)-carboxymethyl substituent, when the latter is equatorial. Indeed, the effect is so pronounced and destabilizing in this particular system that it actually causes the piperazic acid ring to flip into the chair conformation that places the adjacent \textit{C\textsubscript{3}}-carboxymethyl substituent axial and H3 equatorial.\textsuperscript{1} In the case of an N(1)/N(2) doubly N-acylated piperazic acid derivative like 6, such rotameric strain is further exacerbated by the multiple competing C=N rotameric equilibria that actually exist and the substantial bulk of the two adjacent N-Boc groups.

It should be no surprise therefore to find that N(2)-substituted-piperazic acid residues within various cyclopesptide natural
products are typically associated with an axial C3-carboxamide group; a fact that has long been appreciated by the cogniscenti of the cyclodepsipeptide field since the early 1970s, but which has never been quite so explicitly stated or explained previously. Similar arguments hold for the N(2)-acyl N(1)-dehydropropionazic acid-containing cyclodepsipeptides such as the luzopeptins, where the C3-carboxamide again prefers to sit pseudoaxially. We now term this general phenomenon, the A\textsuperscript{1,3} rotamer effect, due to it describing a special hidden type of allylic A\textsuperscript{1,3} strain\textsuperscript{5} that derives from a dynamic exocyclic rotameric C=N double bond interacting with a substantially sized adjacent "pseudoaxially" substituent. An identical type of A\textsuperscript{1,3}-strain has previously been recorded by Johnson for α-functionalized N-acyl piperidines.\textsuperscript{15}

Notwithstanding the unambiguous structural assignment that we had made for 6, obtained via the NCS/Ph3P method, we decided to further secure our assignment. Thus 6 was converted into the N(1)-(2′-4′)-dinitrophenyl-(3S,5R)-5-chloro-piperazic acid methyl ester 7 by trifluoroacetic acid-induced Boc-cleavage in CH\textsubscript{2}Cl\textsubscript{2}, and subsequent N(1)-alkylation with 2,4-dinitrofluorobenzene, in EtOH containing sodium bicarbonate; the two steps proceeded in 81-89% overall yield. Compound 7 had a very well resolved 400 MHz \textsuperscript{1}H NMR spectrum in CDCl\textsubscript{3} (see the SI) and, importantly, removal of the N(2)-acyl group now led to the \textsuperscript{1}C\textsubscript{6} chair conformation becoming dominant, wherein the C(3)-carboxymethyl was equatorial and the C(5)-chloride substituent was axial, as anticipated based solely on A-values. Evidence for this assignment came from the broadened axial H4 ddd at \(\delta\) 2.12 which had \(J\) values of -13.6, 10.4 and 2.6 Hz respectively. The equatorial H(4) resonance also appeared as a ddd at \(\delta\) 2.29. Its multiplicity readily allowed the geminal H4axH4eq coupling constant to be estimated as \(ca. -13.8\) Hz. In addition, the H-5 signal at \(\delta\) 4.55 appeared as a broadened apparent quintet with a \(J\) value of approximately 3.7 Hz, which indicated that this proton was equatorial and the C(5)-chloride substituent was axial. Collectively, these \(J\) values meant that \(J\text{H3axH5ax}\) had to be 10.4 Hz and that the averaged \(J\text{H4axH4eq}\) was \(ca. 3.2\) Hz. Together, these \(J\) values confirmed the 3,5-trans-relative configuration for this isomer within a \textsuperscript{1}C4 chair, which is what one would expect after the N(2)-acyl substituent had been removed (vide infra).

We next examined the PhP/CCl\textsubscript{3}/MeCN mediated chlorination of the trans-configured (3R,5S)-configured alcohol 1, claimed to have been studied by Shin et al.\textsuperscript{b} in their paper. In our case, we independently synthesized 1 via a completely new and unambiguous route that was adapted from our earlier work (Scheme 2).\textsuperscript{3,9} Importantly, we found that the 3,5-trans-alcohol 1 underwent a clean S\textsubscript{2}2 inversion of configuration when submitted to the aforementioned chlorination conditions, to give the desired 3,5-cis-chloride 13 as the sole reaction product in 92% yield.\textsuperscript{3,9}

Yet again, extensive line broadening was evident for many of the resonances in the \textsuperscript{1}H spectra of 13, recorded in a range of NMR solvents (see SI). Fortunately, however, the 400 MHz \textsuperscript{1}H NMR spectrum of 13 in CDCl\textsubscript{3} did give rise to a reasonably well resolved apparent quintet for H-5 at \(\delta\) 4.19, for the major chair conformer present in solution; it had a \(J\) value of \(ca. 3.1\) Hz, which suggested that a \textsuperscript{3}C\textsubscript{3} chair was being adopted in which the C(5)-Cl was axial. The axial H-4 atom of this major conformer also resonated as a broadened ddd at \(\delta\) 2.19; it had approximate \(J\) values of -14.2 (\(J\text{H4axH4eq}\)), 6.8 (\(J\text{H4axH4eq}\)) and 3.4 Hz (\(J\text{H4axH3eq}\)). The latter observations were only compatible with a slightly flattened chair in which H(3) was essentially equatorial and the C(3)-carboxymethyl was essentially axial, as one would expect from the combined operation of the rotameric A\textsuperscript{1,3} effect and N-inversion.

The alternative minor chair conformer could also be detected in this 7:1 mixture of chair conformers. Significantly, the H-4ax resonance for the minor chair conformer appeared as a large apparent quartet of overall width 36 Hz. This argued that these large and fairly similar \(J\) values were contributing to the overall splitting. As demonstrated, this minor conformer was the alternative cis-3,5-configured \textsuperscript{3}C\textsubscript{3} chair in which the C(3)-carboxymethyl and C(5)-Cl were now both equatorial. Presumably this minor chair conformer is observable for 13 because of the significant 1,3-diaxial interaction that exists across the ring when these substituents are both axial.

Even so, to place our absolute stereochemical assignment beyond any doubt at all, we converted 13 into the cis-configured N(1)-(2′-4′)-dinitrophenyl (3R,5R)-5-chloro-piperazic acid methyl ester derivative 15 (Scheme 2). 400 MHz \textsuperscript{1}H NMR spectroscopy of 15 in CDCl\textsubscript{3} now very clearly revealed that the all cis-configured (3R,5R)-5-Cl-Piz derivative had indeed been prepared (see SI). Specifically it showed that the \textsuperscript{3}C\textsubscript{3} chair conformation was now being adopted in which the C(3)- and C(5)-substituents were both equatorial. This assignment was secured by the large diaxial coupling constants observed for \(J\text{H4axH5ax}\) and \(J\text{H5axH6ax}\). In this regard, the signal for the axial H-4 proton at \(\delta\) 1.73 was an apparent quartet with fairly broad lines, even on heating to 50 °C. The width of this apparent quartet was 36.3 Hz demonstrating that these three large coupling constants of roughly similar magnitude (\(ca. 12.1\) Hz) were contributing to the splitting. The partnering H(4) equatorial peak was a doublet of apparent triplets at \(\delta\) 2.61, which allowed estimation of the geminal coupling constant as -12.4 Hz. Therefore the sum of the two vicinal coupling constants in the axial H4-multiplet was 23.9 Hz, but due to the broadness of the signals (line width 3 Hz), these two values could not be determined with precision. Nonetheless, spectral simulation revealed that a difference in vicinal coupling constant of 2.6 Hz could be identified in the measured spectra so that the other two \(J\) values had to be \(ca. 11.95\) Hz (± 1.3 Hz). All values in this range are consistent with diaxial coupling which proved that the relative configuration of 15 must be cis, with the chloro and carbomethoxy groups both occupying equatorial positions.

A careful re-examination and comparison of Shin and coworkers’ reported spectral and optical rotation data for their claimed (3R,5S)-trans-2,5 with our own data for the (3S,5R)-

Scheme 2. Our unambiguous synthesis of (3R,5S)-Cis-5-Cl-piperazic acid derivatives.
trans-6 enantiomer, reveals that Shin and coworkers have actually prepared (3S,5R)-trans-6, rather than the (3R,5S)-trans-2 claimed in their paper, and our combined halogenation studies prove that the former must have originated from the (3S,5S)-cis-configured alcohol 3, whose synthesis has not been formally described by Shin et al. in reference 6. In addition, the spectral and [α]D data that Shin et al. report for the cis-3,5-chloride 13 are irreconcilable with the 3,5-cis stereochemistry that they claim. They also do not match with the NMR data that we have independently obtained for authentic 13 in d6-DMSO (see our SI). Indeed, the 1H NMR spectrum and [α]D measurement for their claimed cis-(3R,5R)-5-CI-Piz derivative 13 appear to more reasonably agree with the data for the (3S,5R)-trans-chloride 6 that we have synthesized from 3 by the Ph3P/NCS and Ph3P/CCl4/MeCN methods (see our SI for the spectral comparison). The cis (3R,5R)-5-Piz chloride 13 that the Shin group have laid claim to, has, in our opinion, simply not been prepared by this team. Our present report thus constitutes the first unambiguous total synthesis of an enantiopure 3,5-cis-configured 5-chloro-Piz derivative that has knowingly been synthesized.

Since a number of bromomonamycin natural products4 are also now known, we considered it important that we definitively synthesize the cis-5-bromo- and 5-ido-piperazic acid derivatives 16 and 17, via our approach (Scheme 3), to place their stereochemical assignments on a secure footing. Our results are presented below. The key point that we wish to make here is that the Ph3P-mediated bromination and iodination processes on 1 (including with Ph3P/NIS; see SI) both proceed with S2 inversion of configuration, as one would expect. Likewise, inversion was also observed in the Ph3P/CCI4/MeCN mediated chlorination of 22 to obtain 23, which was thereafter converted into 24.

Scheme 3. Our unambiguous synthesis of various (3R,5R)-Cis-5-halogeno-piperazic acid derivatives.

Given the stereochemical misassignments of Shin et al., this does of course mean that the recently published synthetic work of Lindsley and Kennedy10 on piperazimycin A must now be fully reexamined and possibly revised, since these workers have unacceptably relied upon the now defunct Shin retentive Ph3P/NCS chlorination of 14 in their claimed synthesis of the dipeptide 25. In light of the problems that we have identified, it would appear that Lindsley and Kennedy10 have most likely synthesized the dipeptide 26 rather than 25. However, we cannot be absolutely certain of this presently due to the lack of J values and multidimensional NMR assignments in their report.10

In conclusion, we have now demonstrated that the tandem asymmetric electrophilic hydration-nucleophilic cyclization method developed in our laboratory19 for piperazic acid synthesis can successfully be applied for the stereocontrolled synthesis of either 3,5-cis- or 3,5-trans-5-halo-piperazic acid derivatives in enantiopure form. We have also proven that N(1), N(2) or C(3)-CO2Me mediated neighboring-group participation does not occur in the Ph3P-mediated halogenation of 5-hydroxy-N(1),N(2)-(di-N-acetylated piperazic acid derivatives, nor do these substitutions proceed via the S2 mechanism. Indeed, such reactions always proceed with stereochemical inversion,12 as was indicated in our 1998,20001 and 2011 literature reports. We have also provided here, for the very first time, an unambiguous explanation of how the rotameric A13-effect can dramatically affect piperazic acid ring conformation in N(2)-acyl piperazic acid derivatives,14 and we have definitively shown how this effect can force the adoption of a seemingly disfavored chair that places the C(3)-carboxy in an axial orientation. Similar effects undoubtedly operate in related systems such as N-acyl piperidic acids.15 We hope that our latest work will now restore clarity to the area of 5-hydroxy-Piz halogenation5,8 which had become rather muddled10 following the publications of Shin et al.6 and Lindsley and Kennedy.10

Acknowledgments

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References and Notes


References and notes

8. Kennedy, J. P.; Brogan, J. T.; Lindsley, C. W. Tetrahedron Lett. 2008, 49, 4116. In this paper, Lindsley et al. use the Ph3P, CCl4, MeCN method of the Hale group (ref. 5a) for S2,2 invertive chlorination of a cis-(3R,5R)-configured Piz alcohol to obtain the trans-configured protected (3R,5S)-5-Cl-Piz derivative; this work of Lindsley is therefore likely correct.


Supplementary Material

Copies of the 400 MHz 1H and 100 MHz 13C NMR spectra are supplied for all the new and previously unreported intermediates described in this route.