
Kevin F. McGee, Jr.,1 Taleb H. Al-Tel,2 Scott McN. Sieburth*
Department of Chemistry, State University of New York, Stony Brook, New York 11794–3400, USA
Fax +1(631)6328882; E-mail: scott.sieburth@sunysb.edu
Received 5 March 2001; revised 29 March 2001
Dedicated to Howard Zimmerman on the occasion of his 75th birthday

Abstract: Intramolecular photocycloaddition of a three-carbon tethered pyrindinone–pyridone system yields the 5-8-5 ring system of the fusicoccin/ophiobolin/ceroplastol families. The stereoselectivity of the cycloaddition was found to be dependent on nitrogen substitution; N-methylation led to exclusively trans products while an absence of nitrogen substitution resulted in solvent-dependent stereoselectivity. Solvent and concentration effects for this cycloaddition were consistent with a hydrogen-bonded dimer that enforces a pro-cis conformation in nonpolar solvents and at higher concentrations. The cis-isomer, a fusicoccin synthesis intermediate, underwent a Cope rearrangement at ambient temperature but could be trapped efficiently as the mono epoxide, yielding a product with six new stereogenic centers. A four-step transformation of an amide carbonyl to a methyl group was achieved using a carbamoyl group to activate the amide for cleavage.

Keywords: fusicoccin, higher-order cycloadditions, photochemistry, stereoselectivity, solvent effects

Among the cyclooctane-containing natural products, more than 60 members have a tricyclic 5-8-5 carbon skeleton, divided largely among three families: the fusicoc- cins, the ophiobolins, and the ceroplastols (Scheme 1). These families are differentiated as di- or sesterterpenes and by their stereochemistry, but have a number of obvious structural similarities. For example, all of these substances have methyl groups (or oxidized methyl groups) at C-3, C-7 and C-11 (fusicoccin numbering). Several of these structures have been successfully prepared by total synthesis;3 in this report we describe the use of 2-pyridone photocycloaddition to assemble the central features of the fusicoc- cins.4

The carbon skeleton of the simplest 2-pyridone photodimer consists of a cycloocta-1,5-diene (4), with two one-carbon substituents, the bridging lactam carbonyls. These lactams can be trans (2) or cis (3), with the former typically dominating the product mixture. The exclusively head-to-tail regiochemistry of the cycloaddition results in a terpene-like product that overlaps intriguingly with the cyclooctane of a variety of natural products, including those in Scheme 1.

Intramolecular photoreaction of 5, pyridones tethered head-to-tail by a three-carbon chain (Scheme 2), forms cycloadducts 6 and 7 with fused 5-8 carbon rings. A stereogenic center on the tether at C-12 such as a tert-butyldimethylsilyloxy group, controls formation of the adjacent stereocenter, leading to anti-isomers as the only observed products. This cycloaddition yields, however, a mixture of cis and trans products similar to that formed by intermolecular reactions (Scheme 1).

Adapting this intramolecular photochemistry to give all three carbon rings of the fusicoc- cins required only that one of the pyridones carry a cyclopentane ring (a pyrindinone), 8. Moreover, only two additional appendages would be required in a fusicoccin A precursor, the methoxyethyl group at C-3 and the side chain at C-14. Nevertheless, for intramolecular photochemistry of 8 to be a useful solution to the challenges of a fusicoccin synthesis, additional goals needed to be met, the most important early objective being a cis-selective photocycloaddition. The cis relationship of the methyl groups of fusicoccin A would be ideally addressed with a cis cycloaddition of 8 to give 9. The chemistry of 9 was also anticipated to be challenging: despite decades of study of the 2-pyridone photodimerization, few successful manipulations of 2-pyridone photoproducts had been reported. The initial objec-
tives, therefore, were to devise a way to gain cis selectivity for the photocycloaddition and then to demonstrate that the amide carbonyl groups could be reduced to methyl groups in this densely functionalized system.

Pyridone photodimerizations, and their intramolecular counterparts, yield either mixtures of trans and cis products (Schemes 1 and 2) or exclusively trans products. When this investigation began, cis-selective dimerizations of 2-pyridones had only been observed for reactions performed in micelles. General conditions for trans selectivity have been described, but no equivalent procedure had been developed for cis-selective reactions. Nevertheless, the product mixture formed by 5 indicated that the relative energies of the pro-cis and pro-trans conformations (Figure 1) leading to [4+4] products 6 and 7 must be nearly identical in energy. It seemed reasonable, therefore, that a small change in their relative energies could lead to cycloadditions with high cis selectivity.

Comparing the pro-cis and pro-trans conformations of 8 with those of 5 (Figure 1) suggested that one new interaction would be present in the pro-trans conformation. We have proposed that the polar pyridone carbonyls, at least in hydrogen-bonding solvents, carry a solvation-enhanced steric bulk. This would lead to a steric interaction (shown by the large arrow) for the pro-trans conformation of 8, an interaction not found for 5, whereas inspection of the pro-cis conformations of 5 and 8 reveal no additional interactions. Destabilizing the pro-trans conformation would lead to enhanced production of the cis-isomer.

Notably, the C-3 and the C-12 substituent stereochemistry of 8 were expected to work in concert. For both 5 and 8, the bulky silyloxy group can be pseudo-equatorial when the pyridones are aligned in any cycloaddition-conducive conformation (Figure 1). At the same time, the C-3 methoxymethyl group of 8 blocks one face of the pyridone to which it is attached. These two stereogenic centers would thereby synergistically enforce the same stereochemistry at C-11, but would not play a role in the cis/trans outcome. The cis selectivity of 8 was paramount. To evaluate the anticipated cis selectivity outlined in Figure 1, only the cyclopentene ring was required. We therefore prepared and tested the photochemistry of 10, containing a single stereogenic center.

Synthesis of the pyrindinone-pyridone 10 began with a two-step conversion of cyclopentanone to pyrridinone 11, using a modification of the procedure of Paine (Scheme 3). O-Benzylolation of 11 using Tieckleman’s conditions, followed by reduction of nitrile 12, gave the aldehyde 13. Coupling of aldehyde 13 with the magnesium acetylide followed by derivatization with tert-butyldimethylchlorosilane, gave silyl ether 15. Hydrogenation/hydrogenolysis of 15 with palladium-on-carbon produced bis-2-pyridone 16. Treatment of 16 with excess iodomethane and potassium carbonate in methanol gave N,N'-dimethyl 10.

One of the mono-N-methyl bis-2-pyridines was also prepared (Scheme 4), to evaluate the effect of nitrogen substitution (vide infra). Treatment of nitrile 11 with DIBAL led to its reduction to the aldehyde 17. Using an excess of the acetylide, in part to deprotonate the acidic pyridone proton of 17, led to alcohol 18 in modest yield. Alcohol 18 was then N-methylated, converted to the tert-butyldimethylsilyl ether, and hydrogenated/hydrogenolyzed to give 19.
The proposed cis-selective photocycloaddition was tested with 10 (Scheme 5). To our delight, the cycloaddition was not only rapid (3–4 h) but also gave a single product (proton NMR)! The product was not, however, consistent with the anticipated cis product 20. We have found empirically that proton and carbon NMR spectra provide evidence of the cis/trans stereochemistry. For trans-isomers, the proximity of the amides to the alkenes results in a dispersion of the alkene chemical shifts, whereas for the cis-isomers the alkene chemical shifts are similar. In the case of 21, the 13C chemical shifts for the alkenes are spread over more than 30 ppm. X-ray crystallography confirmed that, despite the expectations outlined above, only the trans-isomer 21 had formed.12 While this was the most trans-selective photocycloaddition we have observed for a three-atom tethered pyridone, the desired cis-selective cycloaddition was clearly not in hand. In keeping with all previously studied pyridone photocycloaddi-

In view of the intransigent stereochemical outcome of pyridone 10 photochemistry, we turned our attention to the effect of pyridone nitrogen substitution. N-Methylation has been routinely used in all of our 2-pyridone photochemistry for several reasons. Photodimerization of pyridones lacking nitrogen substitution often leads to products that are highly insoluble.13-15 Tethered pyridones without nitrogen substitution have been used for molecular self-assembly,16 because nitrogen-unsubstituted pyridones strongly associate through hydrogen bonding. Nitrogen-unsubstituted 2-pyridones therefore tend to be very polar and of low solubility. Nevertheless, the ready availability of intermediate 16 made evaluation of its properties straightforward.

The stereoselectivity of 16 proved to be highly responsive to the reaction solvent,17 the first substantial solvent dependency found for any 2-pyridone photocycloaddition. In addition, the stereoselectivity was also affected by the concentration of 16.18 These effects are illustrated in Scheme 6 and tabulated in the Table. For polar solvents like methanol or DMSO, a high percentage of the trans photoproduct 22 was produced (1–10% cis), whereas in benzene or toluene, the cis-isomer 23 is essentially the only product observed (>99% cis). Increasing the polarity of the solvent from benzene (ET =34.3)19 to chlorobenzene (ET =36.8) and trifluoromethylbenzene (ET =38.5) decreases the cis selectivity to 95% and 80%, respectively. Use of dichloromethane (ET =40.7) yields mostly the trans-isomer (25% cis).

If hydrogen-bonding solvents are used, the cis selectivity is much lower. Diethyl ether, although less polar (ET =34.5) than chlorobenzene, leads to a 67% cis product mixture. THF (ET =37.4) and ethyl acetate (ET =38.1) both produce a 50–80% cis mixture.
These selectivities were determined using a 25 mM starting concentration of 16. With highly cis-selective solvents like chlorobenzene, decreasing the concentration by two orders of magnitude fails to alter the percentage of cis-isomer formed. Changing the concentration in THF or ethyl acetate, however, leads to substantial changes. Low concentrations (i.e. 0.05 mM) yield mostly the trans-isomer, whereas high concentrations (50 mM) yield mostly the cis-isomer.

These concentration and solvent polarity responses are consistent with a hydrogen-bonded dimer of 16 (Scheme 7). Wuest has investigated head-to-tail tethered pyridones similar to 16 and found that they formed hydrogen-bonded dimers and trimers. In the 1H NMR spectra of 16 in chloroform, THF and benzene, the two different hydrogen-bonding protons were visible as broad but well defined singlets near 14 ppm, consistent with the observations of Wuest for his self-assembling bis-2-pyridones. A hydrogen-bonded dimer of 16, with four hydrogen bonds, aligns the pyridones of each molecule in the same direction. Folding this dimer puts both molecules in a pro-cis conformation that leads to cis photoproducts. The cis photoproducts, moreover, likely template other molecules of 16 into a pro-cis conformation.

Nitrogen substitution on both pyridones would, of course, make the hydrogen-bonded dimers of Scheme 7 impossible, but would a single N-methyl group be sufficient to eliminate formation of the cis-isomer? This question was addressed with the mono-N-methyl 19 (Scheme 4). Interestingly, the presence of single methyl group completely eliminated the solvent dependency of the cycloaddition; photoreaction of 19 gave only the trans product, whether the reaction solvent was methanol or benzene. While the reason for the high trans selectivity of the nitrogen-substituted pyridones 10 and 19 remains obscure, the excellent cis selectivity of 16 set the stage for transformations of the functionally dense 23.

One problem remained with this cis-selective reaction, a surprising instability of the product 23. Many multiply bridged 1,5-dienes with the alkenes in close proximity, including the cis-pyridone dimers, undergo a facile Cope rearrangement. The unusual direction of this rearrangement has been noted previously. The parent cis-1,2-divinylcyclobutane, on warming to 120°C, rearranges to 1,5-cyclooctadiene. In contrast, the 1,5-cyclooctadiene of 23 rearranges quantitatively to the divinylcyclobutane overnight at ambient temperature (Scheme 8). This is the most facile rearrangement of a pyridone photoproduct that we are aware of, and may reflect either a more strained product, with the added substitution of the

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**Scheme 6** Solvent and concentration dependence for the photocycloaddition of 16. Dark bars indicate non-hydrogen-bonding solvents

**Table** Percent cis-23 Formed by Photocycloaddition of 16 as a Function of Solvent and Concentration

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$E_T$</th>
<th>50 mM</th>
<th>25 mM</th>
<th>5.0 mM</th>
<th>0.5 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_2$H$_6$</td>
<td>34.3</td>
<td>&gt;9 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>34.5</td>
<td>6 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTBE</td>
<td>35.5</td>
<td>90 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhCl</td>
<td>36.8</td>
<td>95 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>37.4</td>
<td>57 %</td>
<td>53 %</td>
<td>42 %</td>
<td>27 %</td>
</tr>
<tr>
<td>EtOAc</td>
<td>38.1</td>
<td>7 %</td>
<td>7 %</td>
<td>67 %</td>
<td>31 %</td>
</tr>
<tr>
<td>PhCF$_3$</td>
<td>38.5</td>
<td>80 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>40.7</td>
<td>25 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>45.1</td>
<td>&lt;2 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeOH</td>
<td>55.4</td>
<td>10 %</td>
<td></td>
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</tr>
</tbody>
</table>
cyclopentane ring, or stabilization of a polar transition state: early heterolytic cleavage of the C-6–C-7 bond (Scheme 7) in 23 would create an iminium/enolate zwiterion, shown in an extreme form as 26.21–23 The alkyl substitution at C-6 would stabilize positive charge at this position, lowering the energy of this transition state and consequently the rate of reaction. Whatever the cause of the rearrangement facility, this unstable product would somehow need to be stabilized or intercepted. In earlier work on the taxol problem,24 we had found that hydrogenation of an alkene stabilized the [4+4] adduct and we expected that removal of one alkene of 23 would have the same result.

After much experimentation, it was discovered that dimethyldioxiirane (DMDO)25,26 was an ideal reagent for capturing 23. Irradiation of 16 in toluene for three hours at 0 °C led to a single and stable product 25, isolated in 84% overall yield from 16 (Scheme 8). With only one olefin proton in the 1H NMR spectrum, epoxidation had occurred at the disubstituted and not the trisubstituted alkene. This selectivity may be due to the steric sensitivity of DMDO27 and the shielding of the trisubstituted alkene by the nearby silyloxy group. Approach of the DMDO was assumed to have occurred from the least hindered face of the alkene. These assignments were confirmed by X-ray crystallography of a more advanced intermediate (see Figure 2). The site of this epoxidation was ideal for fusicoccin A, situated where a trans-1,2-diol is located in the natural product (Scheme 1).

With the stable, cis-cycloadduct 25 now in hand, the next objective was reduction of the amide carbonyl groups to methyl groups. At the start of this project, few reactions of 2-pyridone dimers were known. Paquette had reported the most substantial transformations, alkene hydrogenation, amide reduction to tertiary amines, and quaternization of the amines,14,35 but in no case had photodimer amine bonds been opened, hydrolytically or reductively. In our recent work with [4+4] adduct 27, however, Grieco’s cleavage procedure for secondary amides28 had worked extremely well; Boc-activated amide 28 formed rapidly, and reductive opening with lithium borohydride to 29 proceeded smoothly.29,30 Despite this precedent, intermediate 25 proved to be impervious to derivatization with a Boc group, a tosylate group, or even a mesylate group. Presumably this is due, in part, to the neopentyl nature of the nitrogens in 25. In addition, while one face of the secondary amide of 27 is blocked by an alkene, the amides in 25 are buttressed on one side by an amide group, which presents a greater steric hurdle. We turned, therefore, to the use of an isocyanate, a compact, unencumbered functional group. Scheme 9 shows a Chem3D model of the expected approach of methyl isocyanate to an amide nitrogen in 25. This transformation proved quite successful. Following treatment with sodium hydride, introduction of several different isocyanates gave nitrogen adduct 30 in good to excellent yields.

Interestingly, in each of these reactions a single isocyanate product was found, having reacted only once and with only one of the two amides. The differences in the amide environments are rather subtle, making a prediction of the reaction site tenuous. The single derivatization is easier to understand. An approach of the isocyanate to the anion of 25 that minimizes steric interactions would be nearly orthogonal to the plane of the amide (Scheme 9). This trajectory requires that one end of the isocyanate be directed toward the other amide. If that amide is nitrogen-substituted, sterics might preclude such an approach. The first isocyanate reaction would therefore be expected to slow or prevent a second isocyanate reaction.

Identification of the site of the isocyanate reaction, near the trisubstituted alkene, was conclusively determined by X-ray crystallography of the isopropyl derivative (Figure 2).31 This structure also confirmed the cis stereochimistry of the cycloaddition, the relative stereochimistry of the silyloxy substituent, and the site and stereochimistry of the epoxidation. In addition, an intramolecular hydrogen bond was found between the carbamoyl nitrogen and the imide carbonyl oxygen with an H–O bond length of 1.94 Å. This proton was clearly visible in the proton NMR spectrum of 30, as a well defined, albeit broad, singlet at δ=8.1.

With successful introduction of a carbamoyl-activating group, reductive cleavage of the imide carbonyl of 30 was anticipated to be straightforward. Carbamoyl-activated amides have been opened with a variety of nucleophiles, including hydride.32 While reduction of a γ-lactam activated with a carbamoyl group closely related to 30 had not been reported, the reactivities of a broad series of related amide and carbamate systems appeared to be sufficient precedent.

Scheme 8  cis-Product 23 undergoes a facile Cope rearrangement, but can be efficiently intercepted by epoxidation with dimethyldioxiirane. An early bond cleavage in 23 would lead to zwitterionic 26.
Treatment of 30, R=Ph, with NaBH₄ following Katigiri’s procedure, did not lead to any product formation. Lithium borohydride, on the other hand, led almost exclusively to the loss of the carbamoyl group and regeneration of 25! Attack of the hydride on the urea-like carbonyl over the imide-like carbonyl was unexpected. Consideration of the phenyl group electronegativity as well as the conjugation of the nitrogen lone pair into the aromatic ring, made it clear that an aliphatic group would be a better choice as a nitrogen substituent. The isopropyl carbamoyl group was selected for further experimentation, with the expectation that it might also provide a degree of steric protection for the urea carbonyl carbon.

Reduction of 30, R= i-Pr, did lead to the desired cleavage mode, yielding 31, however, competitive cleavage of the carbamoyl group remained problematic. Although byproduct 25 was easily recycled, minimizing its production was obviously the best alternative. The ratio of 25 and 31, the only products formed, was eventually found to correlate with the initial concentration of lithium borohydride. When the concentration of LiBH₄ was held at 0.4 M and the concentration of 30 at 40 mM, a consistent 64% yield of 31 was achieved, whereas higher or lower concentrations of LiBH₄ led to reduced yields (Scheme 10). We are not aware of any similar reports of the effect of LiBH₄ concentration on a reduction outcome.

It was possible that the 25/31 ratio is related to the conformation of the carbamoyl group and perhaps chelation of lithium by the two carbonyls. Attempts to modulate the reaction with additives, including LiCl, ZnCl₂ and MgBr₂, failed to positively impact the yield of 31.

The reduction of the amide carbonyl dramatically altered the chemical shift of the C-12 carboxyl proton geminal to the silyloxy group. In 30 (and earlier compounds) this proton is visible in the ¹H NMR spectra at δ=4.8 ± 0.3, anomalously far downfield, due to the anisotropy of the nearby amide carbonyl. Reduction of this carbonyl to give 31 is accompanied by a change in the chemical shift of this proton to the more typical 3.4 ppm, an upfield movement of 1.4 ppm.

Figure 2 Crystal structure of isocyanate derivative of 25 showing intramolecular hydrogen bond

Scheme 9 Activation of the secondary amides of the [4+4] adducts allows for facile amide opening. While 25 was inert to the standard reagents, an isocyanate adduct was readily formed. A molecular model shows approach of an isocyanate to the amide.

Scheme 10 Lithium borohydride reduction of 30 was a competition between carbonyl reductions a and b. The yield of 31 correlated with the initial concentration of lithium borohydride.
Successful reduction of the amide carbonyl set the stage for conversion of the alcohol in 32 to a methyl group. The neopentyl setting of this alcohol, with the surrounding functionality, was anticipated to provide multiple reaction pathways. Nevertheless, treatment of 31 with methanesulfonyl chloride produced the mesylate 32 without difficulty. This mesylate, when heated to 110 °C in DMF containing NaI and zinc powder, 33,34 gave a clean conversion to 33 in a gratifying 90% yield (Scheme 11).

Attaining product 33 fulfilled the objectives of developing a cis-selective cycloaddition and demonstrating that the photoproduct amides could be readily reduced to methyl groups. The limitations of product 33, with its rather rigid bridged cyclooctane and without the additional functionality required for the natural product, meant that it had reached the end of its usefulness as a fusicoccin model. The successful completion of the objectives set out at the beginning, however, provides a firm platform from which to build a total synthesis, and progress in this arena will be provided in due course. Notably, the six steps from 10 to 33, Scheme 12, includes the first cis-selective pyridone cycloaddition, presumably generalizable to related systems, and the first reduction of an amide to a methyl group in a polycyclic pyridone photoproduct.

**Scheme 11** Two-step reduction of the hydroxymethyl to a methyl group

2-Oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carbonitrile (11)\(^9\)

To a flask charged with finely cut sodium metal (2.24 g, 97.5 mmol) in Et\(_2\)O (175 mL) at 0 °C was added dropwise a solution of cyclopentanone (10.5 mL, 119 mmol) and ethyl formate (10 mL, 124 mmol) in Et\(_2\)O (100 mL) over the course of 40 min. After stirring overnight, the brown slurry was filtered, the residue washed with Et\(_2\)O (2 × 150 mL), and dried in vacuo to give 8.35 g (63%) of the sodium salt of 2-formyl cyclopentanone as a tan solid.

\(^{1}\)H NMR (DMSO-\(d_6\)); \(\delta = 8.88\) (s, 1 H), 2.25 (t, \(J = 7.5\) Hz, 2 H), 1.88 (t, \(J = 7.5\) Hz, 2 H), 1.57 (pentet, \(J = 7.5\) Hz, 2 H).

\(^{13}\)C NMR (DMSO-\(d_6\)); \(\delta = 195.0, 174.2, 106.0, 39.8, 26.4, 19.8\).

IR (KBr); \(v = 2949, 2836, 1489, 1353\) cm\(^{-1}\).

MS (EI); \(m/\ell (\%) = 112 (15), 84 (39), 55 (100)\).

This salt (8.35 g, 62.3 mmol) and 2-cyanoacetamide (11.5 g, 137 mmol) were suspended in toluene (300 mL) and stirred vigorously as a 1 M solution of AcOH–piperidine (1:1) in CH\(_3\)Cl\(_2\) (27 mL) was added. The mixture was heated to reflux for 2 h, cooled to 0 °C, acidified with AcOH to pH 5 and concentrated in vacuo. The residue was washed with toluene (2 × 100 mL) in vacuo, and purified by flash chromatography (MeOH–CH\(_2\)Cl\(_2\); 1:4) to give 7.9 g (79%) of 11 as yellow solid; \(R_f = 0.7\) (MeOH–hexanes, 1:1).

IR (KBr); \(v = 3002, 2949, 2836, 1638, 1489, 1353\) cm\(^{-1}\).

MS (EI); \(m/\ell (\%) = 160 (M^+, 82), 159 (100), 131 (38), 104 (40), 77 (36), 52 (35)\).

2-(Benzylxoy)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (12)

To a suspension of 11 (1.3 g, 8.12 mmol) and benzyl bromide (2.8 g, 16 mmol) in toluene (43 mL) and protected from light, was added AgCO\(_3\) (1.12 g, 4.06 mmol), and the mixture was stirred for 4 d. The mixture was filtered through Celite, the filtrate concentrated in vacuo, and purified by flash chromatography (CH\(_2\)Cl\(_2\)–hexanes, 1:1) to give 12 (1.94 g, 95%) as colorless crystals; mp 62–64 °C; \(R_f = 0.5\) (CH\(_2\)Cl\(_2\)–hexanes, 1:1).

\(^{1}\)H NMR (CDCl\(_3\)); \(\delta = 7.76\) (s, 1 H), 7.44 (br s, 1 H, NH), 3.02 (t, \(J = 7.5\) Hz, 2 H), 2.79 (t, \(J = 7.5\) Hz, 2 H), 2.20 (pentet, \(J = 7.5\) Hz, 2 H).

\(^{13}\)C NMR (CDCl\(_3\)); \(\delta = 164.0, 158.0, 145.2, 122.0, 116.0, 100.0, 31.8, 29.3, 23.0\).

IR (KBr); \(v = 3002, 2949–2553, 2225, 1649, 1596, 1393, 771\) cm\(^{-1}\).

MS (EI); \(m/\ell (\%) = 160 (M^+, 82), 159 (100), 131 (38), 104 (40), 77 (36), 52 (35)\).

Exact Mass (M\(^+\)); \(m/\ell = 252.1107\), Calcd 250.1106.

2-(Benzoyloxy)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbaldehyde (13)

To a solution of 12 (500 mg, 2 mmol) in CH\(_3\)Cl\(_2\) (20 mL) at −78 °C was washed with a sat. solution of Rochelle’s salt, and the aqueous solu-
6.82 (d, J = 1.1 Hz, 1 H), 7.50–7.57 (m, 9 H), 7.09 (d, J = 7.2 Hz, 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 6.18 (s, 1 H), 5.63 (AB quartet, J$_{ab}$ = 12.5 Hz, Av AB = 12.5 Hz, 2 H), 5.48 (s, 2 H), 3.05 (t, J = 7.5 Hz, 2 H), 2.98 (t, J = 7.2 Hz, 2 H), 2.26–2.17 (m, 2 H), 1.11 (s, 9 H), 0.41 (s, 3 H), 0.31 (s, 3 H).

13C NMR (CDCl$_3$): δ = 163.5, 162.0, 159.4, 140.1, 138.6, 137.9, 137.3, 132.7, 129.6, 128.5, 128.4, 128.3, 128.0, 127.6, 121.0, 120.7, 111.4, 89.4, 84.2, 67.8, 67.6, 60.2, 34.2, 30.2, 26.0, 23.5, 18.5, −4.2, −4.6.

Exact Mass (MH$^+$): m/z Calcd 577.2886, Found 577.2886.

3-[1-[(tert-Butyl(dimethyl)silyloxy)-3-(6-oxo-1,6-dihydropyridin-2-yl)propyl]-1,5,6,7-tetrahydro-2H-cyclopenta[b]pyridine-2(1H)-one (16)

To a solution of 15 (774 mg, 1.34 mmol) in EtOH (8 mL) and EtOAc (11 mL) was added 10% Pd/C (77 mg) and then placed under a pressure of 1 atm. After 5 h, the mixture was filtered through Celite, concentrated in vacuo and purified by flash chromatography (MeOH–CH$_2$Cl$_2$: 1:9) to give 16 (335.4 mg, 62%) as a colorless foam; Rf 0.45 (MeOH–CH$_2$Cl$_2$: 1:9).

1H NMR (CDCl$_3$): δ = 14.2 (br s, 1 H, NH), 13.8 (br s, 1 H, NH), 7.44 (s, 1 H, J = 7.5 Hz, 1 H), 6.32 (d, J = 10 Hz, 1 H), 6.05 (d, J = 7.5 Hz, 1 H), 5.08 (d, J = 5.0 Hz, 1 H), 2.89–2.79 (m, 4 H), 2.68–2.63 (m, 2 H), 2.17–2.04 (m, 4 H), 0.93 (s, 3 H), 0.08 (s, 3 H), −0.05 (s, 3 H).

13C NMR (CDCl$_3$): δ = 166.2, 163.5, 150.6, 147.5, 141.6, 134.4, 132.5, 119.2, 116.2, 105.7, 68.4, 37.9, 30.8, 30.3, 29.8, 25.9, 22.9, 18.2, −4.5.

MS (EI): m/z (%) = 325 (36), 279 (36), 160 (61), 75 (100).

Exact Mass (M$^+$): m/z Calcd 430.2273, found 401.2260.


3-[(1-[(tert-Butyl(dimethyl)silyloxy)-3-[1-methyl-6-oxo-1,6-dihydropyridin-2-yl)propyl]-1-methyl-1,5,6,7-tetrahydro-2H-cyclopenta[b]pyridine-2(1H)-one (10)

To a solution of 16 (257 mg, 0.64 mmol) in MeOH (15 mL) was added K$_2$CO$_3$ (1.77 g, 12.3 mmol) and Mel (1.05 g, 7.38 mmol) and then heated to reflux for 15 h. The reaction was cooled, diluted with EtO$_2$, filtered, and the residue was washed with CH$_2$Cl$_2$ (3 × 15 mL). The combined organics were concentrated in vacuo and partitioned between H$_2$O and CH$_2$Cl$_2$. The organics were concentrated in vacuo and purified by flash chromatography (MeOH–CH$_2$Cl$_2$: 1:9) to give 10 (217.7 mg, 79%) as a colorless solid; Rf 0.65 (MeOH–CH$_2$Cl$_2$: 1:9).

1H NMR (CDCl$_3$): δ = 7.40 (br s, 1 H), 7.27 (dd, J = 6.9, 9.0 Hz, 1 H), 6.65 (d, J = 9.0 Hz, 1 H), 6.20 (d, J = 6.9 Hz, 1 H), 5.01 (dd, J = 3.0, 6.3 Hz, 1 H), 3.54 (s, 3 H), 3.47 (s, 3 H), 2.98 (t, J = 7.5 Hz, 2 H), 2.76 (t, J = 7.2 Hz, 2 H), 2.72–2.65 (m, 2 H), 2.15–2.08 (m, 4 H), 0.91 (s, 9 H), 0.04 (s, 3 H), −0.08 (s, 3 H).

13C NMR (CDCl$_3$): δ = 163.8, 163.1, 150.8, 148.1, 136.6, 132.3, 130.8, 118.2, 116.2, 107.5, 68.8, 58.1, 35.1, 32.4, 32.2, 31.4, 30.5, 29.3, 25.3, 18.1, −4.6, −5.0.

2-Oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxaldehyde (17)

To a solution of 11 (100 mg, 0.62 mmol) in CH$_2$Cl$_2$ (6 mL) at −78°C was added dropwise DIBAL (1.25 mL of a 1 M solution, 1.25 mmol) over 25 min. After 1 h, the reaction was quenched with 10% HCl and stirred for an additional 1 h while warming to r.t. The mixture was washed with sat. Rochelle’s salt, and the aqueous phase was then extracted with CH$_2$Cl$_2$ (3 × 75 mL). The combined organics were washed with brine, concentrated in vacuo, and purified by flash chromatography (MeOH–CH$_2$Cl$_2$: 1:9) to give 17 (80 mg, 78%) as a yellow viscous liquid; Rf 0.6 (MeOH–CH$_2$Cl$_2$: 1:9).

1H NMR (CDCl$_3$): δ = 10.1 (s, 1 H), 7.70 (s, 1 H), 3.00 (t, J = 7.5 Hz, 2 H), 2.78 (t, J = 7.5 Hz, 2 H), 2.19–2.10 (m, 2 H).

13C NMR (CDCl$_3$): δ = 189.2, 165.6, 145.0, 140.0, 133.0, 121.3, 31.9, 22.9, 22.2.

3-[(6-Benzoxylpyrazino-2-yl)-1-hydroxyprop-2-ynyl]-1,5,6,7-tetrahydro-2H-cyclopenta[b]pyridine-2(1H)-one (18)

To a solution of 6-(benzoxylpyrazine) (1.5 g, 7.17 mmol) in THF (10 mL) was added dropwise ethylenemagnesium bromide (7.17 mL of a 1 M solution, 7.17 mmol) over 10 min, and the resulting mixture was allowed to stir for an additional 30 min. A solution of 17 (390 mg, 2.39 mmol) in THF (10 mL) was added dropwise. The reaction was quenched with sat. Na$_2$CO$_3$ and the aqueous phase was then extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organics were washed with brine, dried (Na$_2$SO$_4$), concentrated in vacuo, and purified by flash chromatography (MeOH–CH$_2$Cl$_2$: 1:9) to give...
18 (260 mg, 35%) as a light orange foam; Rf 0.45 (MeOH–
CH2Cl2, 1:9).

1H NMR (CDCl3): δ=7.66 (s, 1 H), 7.49–7.29 (m, 6 H), 7.05 (d, J=7.5 Hz, 1 H), 6.72 (d, J=7.5 Hz, 1 H), 5.73 (s, 1 H), 5.31 (s, 2 H), 3.43 (s, 3 H, OH), 3.00–2.88 (m, 2 H), 2.72 (t, J=7.5 Hz, 2 H), 2.19–2.04 (m, 2 H).

MS (El): m/z (%)=373 (MH+), 20, 357 (85), 251 (68), 161 (100), 91 (42).

Exact mass: m/z Calc 415.2418. Found 415.2416.

1H NMR (CDCl3): δ=7.65–7.29 (m, 7 H), 7.13 (d, J=7.5 Hz, 1 H), 6.74 (d, J=7.5 Hz, 1 H), 5.74 (s, 1 H), 5.36 (s, 2 H), 4.02 (s, OH), 3.52 (s, 3 H, 2.94 (t, J=7.5 Hz, 2 H), 2.81 (t, J=7.5 Hz, 2 H), 2.25–2.13 (m, 2 H).

13C NMR (CDCl3): δ=164.5, 163.2, 158.0, 149.6, 145.0, 138.6, 137.0, 136.6, 128.4, 121.8, 127.9, 126.0, 121.0, 120.7, 120.3, 116.4, 111.6, 100.4, 88.6, 67.8, 67.6, 31.0, 29.2, 22.9.

1H NMR (CDCl3): δ=6.96 (s, 1 H), 7.50–7.29 (m, 6 H), 7.03 (d, J=7.5 Hz, 1 H), 6.69 (d, J=8.3 Hz, 1 H), 5.92 (s, 1 H), 5.34 (s, 2 H), 3.50 (s, 3 H), 2.88 (t, J=7.5 Hz, 2 H), 2.80 (t, J=7.5 Hz, 2 H), 2.18–2.06 (m, 2 H), 0.96 (s, 9 H), 0.28 (s, 3 H), 0.19 (s, 3 H).

13C NMR (CDCl3): δ=7.69 (s, 1 H), 7.50–7.29 (m, 6 H), 7.03 (d, J=7.5 Hz, 1 H), 6.69 (d, J=8.3 Hz, 1 H), 5.92 (s, 1 H), 5.34 (s, 2 H), 3.50 (s, 3 H), 2.88 (t, J=7.5 Hz, 2 H), 2.80 (t, J=7.5 Hz, 2 H), 2.18–2.06 (m, 2 H), 0.96 (s, 9 H), 0.28 (s, 3 H), 0.19 (s, 3 H).

1H NMR (CDCl3): δ=12.68 (br s, 1 H, NH), 7.74 (s, 1 H), 7.28–7.25 (m, 1 H), 6.62 (d, J=7.5 Hz, 1 H), 6.04 (d, J=7.5 Hz, 1 H), 5.03 (t, J=5.0 Hz, 1 H), 3.48 (s, 3 H), 2.88 (t, J=7.5 Hz, 2 H), 2.77 (t, J=7.5 Hz, 2 H), 2.67–2.51 (m, 2 H), 2.18–1.90 (m, 4 H), 0.88 (s, 9 H), 0.02 (s, 3 H), –0.09 (s, 3 H).

13C NMR (CDCl3): δ=164.6, 161.3, 149.4, 148.0, 141.2, 132.7, 131.2, 118.3, 117.0, 104.3, 68.5, 35.6, 32.5, 32.2, 30.5, 28.5, 25.9, 22.4, 18.1, –4.7, –5.0.

MS (El): m/z (%)=415 (MH+), 61, 283 (100).
A solution of 16 (50 mg, 0.12 mmol) in benzene-<sub>d</sub> (2.5 mL) at 5 °C was irradiated for 3 h with a Hanovia 450 W medium pressure mercury lamp in a water-cooled quartz jacket fitted with a pyrex filter. 

1H NMR (CDCl<sub>3</sub>): δ = 8.88 (br s, 1 H, NH), 9.51 (br s, 1 H, NH), 6.14 (br s, 1 H), 5.75 (t, J = 7.5 Hz, 1 H), 5.62 (d, J = 7.5 Hz, 1 H), 5.10 (br s, 1 H), 2.80 (d, J = 7.5 Hz, 1 H), 2.42 (br s, 1 H), 1.98–1.66 (m, 9 H), 0.96 (s, 9 H), 0.10 (s, 3 H), –0.08 (s, 3 H).

(5aR*,6R*,8aR*,12aS*,12bS*,16R*,16aR*)-6-[(tert-Butyl(dimethyl)silyloxy)-2,3,7,8,12a,12b-hexahydro-1H,6H-dicyclope[2.3]pyridin-2(2H,[1,2]pyridine-5,10(4H,9Hf)-dione (24)
An NMR tube containing a 0.025 M solution of 16 (100 mg, 0.4 mmol) in benzene-<sub>d</sub> was irradiated for 3 h with a Hanovia 450 W medium pressure mercury lamp fitted with a pyrex filter. The reaction mixture was then placed in a 45 °C water bath overnight to give 24 in quantitative yield; R<sub>f</sub> = 0.5 (MeOH–CH<sub>2</sub>Cl<sub>2</sub>, 1:9).

1H NMR (CDCl<sub>3</sub>): δ = 11.32 (br s, 1 H, NH), 9.06 (br s, 1 H, NH), 5.89 (d, J = 10 Hz, 1 H), 5.68 (dd, J = 5, 10 Hz, 1 H), 2.59 (t, J = 6.7 Hz, 1 H), 3.34 (d, J = 10 Hz, 1 H), 2.59 (dd, J = 5, 10 Hz, 1 H), 2.36–2.24 (m, 2 H), 1.92–1.22 (m, 8 H), 0.91 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H).

13C NMR (CDCl<sub>3</sub>): δ = 173.2, 164.6, 138.0, 135.3, 122.7, 108.8, 74.4, 67.9, 59.6, 40.4, 37.6, 34.9, 33.5, 31.6, 31.1, 29.7, 25.7, 22.1, –4.8, –4.5.

MS (DCI): m/z (%) = 401 (MH<sup>+</sup>, 100), 329 (25), 279 (39), 269 (100).

Exact Mass (MH<sup>+</sup>): m/z = 411.2406. Found 411.24263.


Following the procedure for 30 (R = i-Pr) using ethyl isocyanate gave the title compound as a colorless solid (92%); R<sub>f</sub> = 0.65 (MeOH–CH<sub>2</sub>Cl<sub>2</sub>, 1:9).

1H NMR (CDCl<sub>3</sub>): δ = 8.17 (br s, 1 H, NH), 6.11 (br s, 1 H), 5.31 (br s, 1 H, NH), 4.83 (t, J = 6.25 Hz, 1 H), 3.44 (t, J = 3.2 Hz, 1 H), 3.36 (s, 1 H), 2.84 (t, J = 6.25 Hz, 2 H), 1.32 (d, J = 2.5 Hz, 1 H), 2.48–1.95 (m, 10 H), 1.14 (t, J = 6.25 Hz, 3 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.05 (s, 3 H).

MS (FAB+): m/z (%) = 510 (MNa<sup>+</sup>, 31), 488 (MH<sup>+</sup>, 12), 392 (3), 219 (5), 165 (7).

Exact Mass (MNa<sup>+</sup>): m/z = 510.2410. Found 510.2400.

Following the procedure for 30 (R = i-Pr) using phenyl isocyanate gave the title compound as a light brown solid (79%); R<sub>f</sub> = 0.65 (MeOH–CH<sub>2</sub>Cl<sub>2</sub>, 1:9).

1H NMR (CDCl<sub>3</sub>): δ = 7.47 (br s, 1 H, NH), 7.88 (br s, 1 H, NH), 7.39–7.27 (m, 5 H), 6.04 (s, 1 H), 4.70 (s, 1 H), 3.39 (t, J = 2.5 Hz, 1 H), 2.90 (s, 1 H), 2.95–1.66 (m, 10 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.03 (s, 3 H).

MS (FAB+): m/z (%) = 558 (MNa<sup>+</sup>, 53), 536 (M<sup>+</sup>*, 30), 417 (9), 285 (15), 165 (13).

Exact Mass (MNa<sup>+</sup>): m/z = 558.2399. Found 558.2399.


Following the procedure for 30 (R = iso-propyl) using cyclohexyl isocyanate gave the title compound as a colorless solid (87%); R<sub>f</sub> = 0.65 (MeOH–CH<sub>2</sub>Cl<sub>2</sub>, 1:9).

1H NMR (CDCl<sub>3</sub>): δ = 8.15 (d, J = 7.5 Hz, 1 H, NH), 6.09 (s, 1 H), 5.49 (s, 1 H, NH), 4.80 (d, J = 5.0 Hz, 1 H), 3.63 (m, 1 H), 3.42 (t, J = 5.0 Hz, 1 H), 3.33 (s, 1 H), 3.09 (d, J = 2.5 Hz, 1 H), 2.47 (s, 2 H), 2.28–1.15 (m, 18 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.04 (s, 3 H).

13C NMR (CDCl<sub>3</sub>): δ = 175.9, 169.7, 152.4, 150.2, 119.6, 73.9, 68.7, 65.5, 65.2, 56.3, 52.8, 49.3, 44.8, 35.2, 32.9, 32.7, 28.8, 25.6, 25.5, 24.6, 24.5, 23.4, 17.8, –4.8, –5.0.

Synthesis 2001, No. 8, 1185–1196 ISSN 0039-7881 © Thieme Stuttgart · New York
To a −10°C solution of 30 (R=iso-propyl, 10 mg, 0.019 mmol) in THF (400 mL) was added dropwise LiBH₄ (100 µL, 2 M in THF) over 1.5 min. After stirring at −5°C for 2 h, the mixture was warmed to r.t. and stirred for an additional 4.5 h. The reaction was quenched with 1 N HCl, extracted with CH₂Cl₂, concentrated in vacuo, and purified by flash chromatography (MeOH-CH₂Cl₂, 1:9) to give 31 (6.4 mg, 64% as a colorless solid; Rᵢ 0.45 (MeOH-CH₂Cl₂, 1:9)).

**References**

(1) Current address: Albany Molecular Research, Inc., Albany, NY 12203, USA.

(2) Current address: Am-Najah National University, Nablus, Palestine.


(4) A portion of this work was the subject of a communication: Siebury, S. McN.; McGee, K. F. Jr.; Altel, T. H. Tetrahedron Lett. 1999, 40, 4007. (b) See also Refs 17 and 18.


(12) Compound 21 crystallizes in the monoclinic space group P2₁/n with a = 10.541(3) A, b = 16.593(2) A, c = 26.791(6) A, β = 90.36(1)°, V = 4686(2) Å³, and Z = 4. Final least squares refinement using 1622 unique reflections with I > 3σ(I) gave R1 (I > 2σ(I)) = 0.060 (0.055).


(30) For a related example that does not involve ring opening when a Boc-activated lactam of a pyridone photodimer is reduced see: Spivey, A. C.; Andrews, B. I.; Brown, A. D.; Frampton, C. S. Chem. Commun. 1999, 2523.

(31) Compound 30 crystallizes from MeCN in the monoclinic space group P2_1/c with a = 15.126(4) Å, b = 12.900(3) Å, c = 15.592(4) Å, β = 111.70(2)°, V = 2826.9(5) Å³, and Z = 4. Final least squares refinement using 2229 unique reflections with I > 3σ(I) gave R1 (wR2) = 0.069 (0.088)


