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Protecting Group Free, Stereocontrolled Synthesis of β-Halo-enamides

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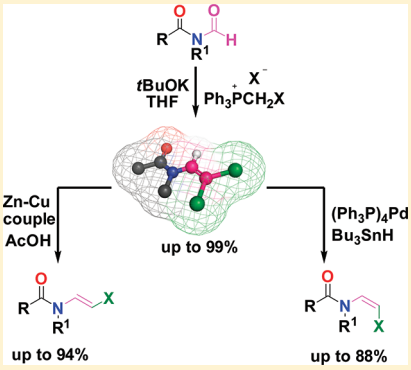
Supporting Information

ABSTRACT: Enamides, dienamides, and enynamides are important building blocks in synthetic, biological, and medicinal chemistry as well as materials science. Despite the extensive breath of their potential utility in synthetic chemistry, there is a lack of simple, high-yielding methods to deliver them efficiently and as single isomers. In this paper, we present a novel, protecting group free, efficient, and stereoselective approach to the generation of β-halo-enamides. The methodology presented provides a robust synthetic platform from which *E*- or *Z*-enamides can be generated in good yields and with complete stereocontrol.



INTRODUCTION

Enamides and dienamides are key intermediates in the synthesis of a variety of heterocyclic compounds.[1] Dienamides have also been used effectively as both electron-rich and electron-poor dienes in Diels–Alder reactions. These dienamide-based Diels–Alder reactions are regioselective and have found application in asymmetric cycloadditions.[2]

Acyclic enamides and dienamides have great synthetic potential and occur widely in nature. For example, biologically active natural products and pharmaceutical leads such as the antibiotic CJ-15,801 **1**, crocacin A **2**, the lituarines **3**, palmerolide A **4**, bacillaene **5**, the retinoidal dienamide **6**, and ariakemicins A **7** and B **8** all contain enamide or dienamide functional groups (Figure 1).[3]

The number of different approaches reported for the synthesis of enamides and dienamides reflects their importance and relevance as target units and functional intermediates in materials, synthetic, and medicinal chemistry.[4] The synthetic methodologies developed thus far enjoy varying degrees of success, particularly with respect to the yield and control of double-bond geometries obtained. Indeed, in a number of cases, there is no control over the geometry of the double bond generated at all.

A reliable and effective methodology with the ability to deliver *E*- and *Z*-β-halo-enamides stereoselectively could be envisaged using di-halo-enamides. These are extremely versatile intermediates, which can provide a viable synthetic platform from which to generate elaborated enamide and dienamides.[5] To date, synthetic approaches toward the synthesis of β-halo-enamides have offered limited flexibility, being primarily focused on the synthesis of the *E*-isomers, largely due to the availability of starting materials. Access to the corresponding *Z*-

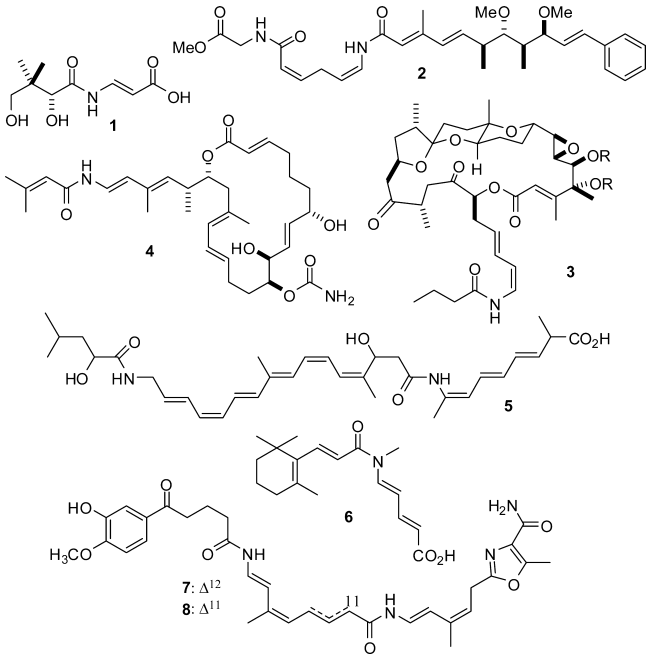


Figure 1. Enamide- and dienamide-containing natural products.

β-halo-enamides has proven to be challenging, and there are no stereoselective methods currently available for their synthesis.[6,7]

As part of this contribution, we now report a novel, flexible, and reliable approach for the convergent and stereoselective

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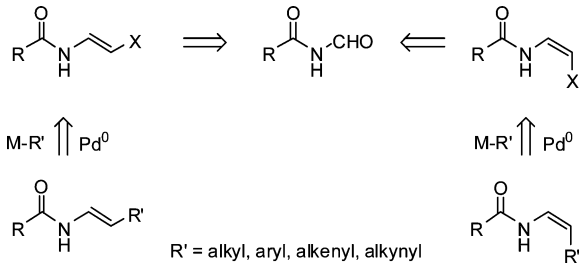
synthesis of geometrically defined β-halo-enamides, starting from simple *N*-formylimides. In turn, this approach provides a viable synthetic platform from which to generate enamides and dienamides in good yield and with excellent stereocontrol (Scheme 1).

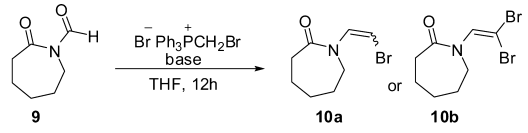
Scheme 1. Proposed Retrosynthesis of Enamides and β-Halo-enamides from *N*-Formylimides



RESULTS AND DISCUSSION

Our approach hinges on the ability of *N*-formylimides to undergo olefination reactions to generate enamides and dienamides in good yield and without the need for nitrogen protection. The *N*-formyl group mimics an aldehyde unit, which allows for the efficient generation of substrates not readily available through any other synthetic means.[8] In our initial studies, caprolactam-derived *N*-formylimide **9** was treated under Stork–Zhao conditions using (bromomethyl)-triphenylphosphonium bromide and a variety of bases with the intention of generating the desired *Z*-bromoenamide.[9] When HMDS bases were employed, despite extensive experimentation, the desired *Z*-bromo-enamide was obtained only in low yields. However, increasing the number of equivalents of phosphonium salt used, and switching the base to *t*-BuOK, resulted in conversion of the *N*-formylimide **9** into the unexpected dibromo-enamide product **10b** in 93% yield (Scheme 2).

Scheme 2. Synthesis of β,β-Dibromo-enamide 10b

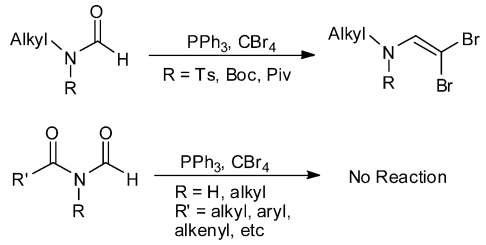


9 10a 10b

Base	$Br^- Ph_3PCH_2Br^+$	Temp.	Yield
NaHMDS (2 eq)	(2 eq)	RT	No Reaction
NaHMDS (10 eq)	(10 eq)	RT	No Reaction
NaHMDS (10 eq)	(10 eq)	reflux	No Reaction
NaHMDS (10 eq)	(10 eq)	RT	**10a** 10% (*E*:*Z* 1:0)
KHMDS (10 eq)	(10 eq)	RT	**10a** 30% (*E*:*Z* 1:1)
LiHMDS (10 eq)	(10 eq)	RT	No Reaction
LiHMDS (10 eq)	(10 eq)	reflux	No Reaction
KO*t*Bu (5 eq)	(5 eq)	RT	**10b** 20% (60% brsm)
KO*t*Bu (10 eq)	(10 eq)	RT	**10b** 93%

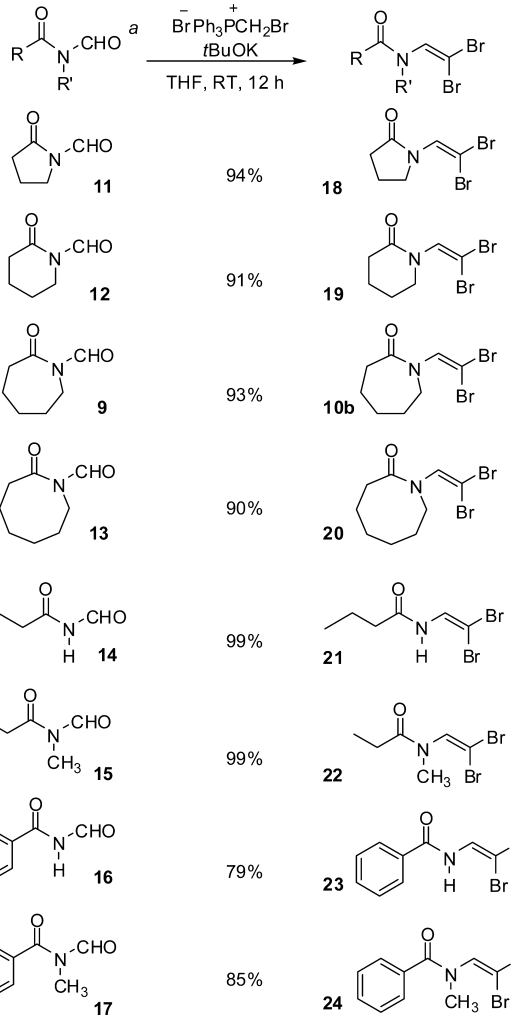
Dibromo-enamides are currently accessed through the use of a Ramirez olefination.[5,10] However, the Ramirez conditions are limited to the dibromo-olefination of formylated tosyl-, Piv-, and Boc-protected amines and are not applicable to unprotected and general imide systems (Scheme 3). Indeed, Lautens and co-workers recently reported that the *gem*-dibromination of formamides only proceeds when an *N*-carbonyl (Boc or Piv) or tosyl-protecting group is present on the formamide.[11]

Scheme 3. Previous Syntheses of β,β-Dibromo-enamides under Ramirez Conditions



We believed that this unexpected and high yielding imide dibromo-olefination reaction could provide a viable synthetic alternative for the synthesis of structurally diverse β,β-dibromo-enamide units. The same bromo-olefination conditions were applied to a range of *N*-formylimides with similar success (Table 1).

Table 1. Effect of Imide Substitution on Dibromo-olefination



[a]All reactions were conducted using 1 equiv of *N*-formylimide, 10 equiv of phosphonium salt, and 10 equiv of base in dry THF (0.33 M) at rt for 12 h.

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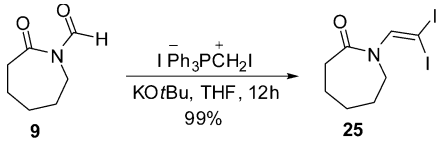
Having obtained encouraging yields and scope for the synthesis of dibromo-enamides, we investigated whether similar results could be obtained with using (iodomethyl)-triphenylphosphonium iodide. Initial iodo-olefination of *N*-formyl imide **9** matched the results obtained during the bromo-olefination and yielded diiodo-enamide **25** in high yield (Scheme 4). The structure of the diiodo-enamide **25** was confirmed by crystallographic analysis (Figure 2).[12]

Scheme 4. Synthesis of *β,β*-Diiodo-enamide 25



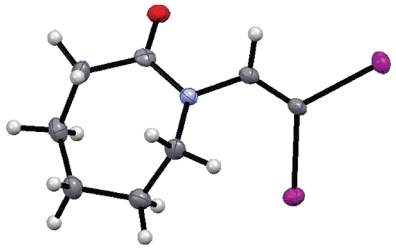


Figure 2. Crystal structure of diiodo-enamide **25**.

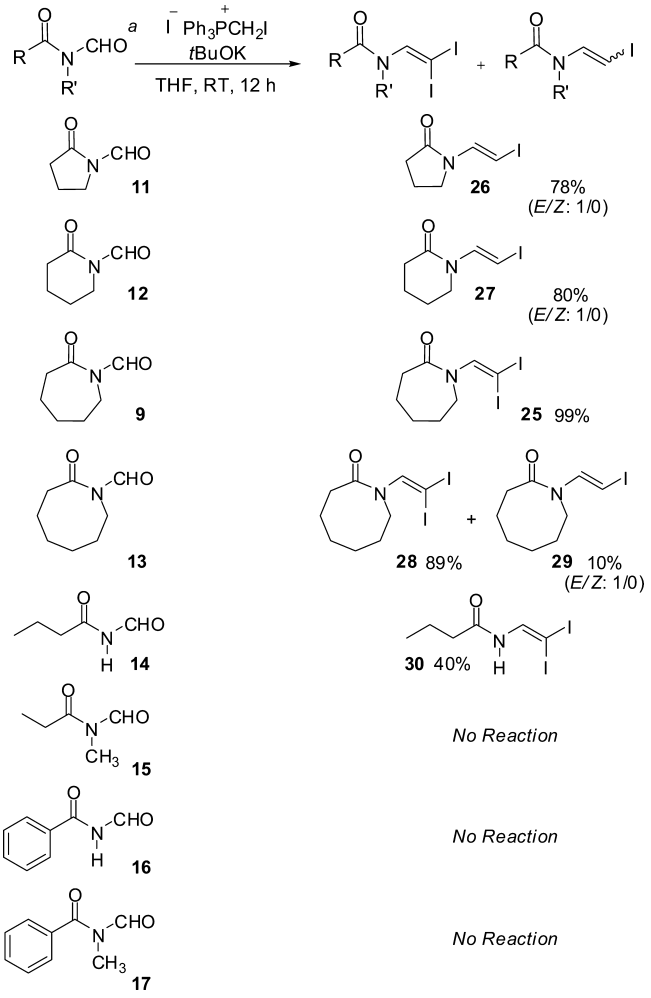
To our knowledge, the only other report in the literature for the synthesis of *β,β*-diiodo-enamides is that of Ferreira and co-workers, who reported the generation of *β,β*-diiodo-enamides in moderate yield by iodination of amino acid derived enamides at 80 °C (Scheme 5).[13]

Application of our same iodo-olefination conditions to the group of *N*-formylimides previously used demonstrated that the iodo-olefination is substrate dependent (Table 2), an observation noted by the Ferreira group in their enamide iodination studies.

For instance, iodo-olefination of *N*-formylimide **13** under the same conditions yielded the diiodo-enamide **28** together with traces of the *E*-iodo-enamide **29**. In contrast, the iodo-olefination of the *N*-formylimides **11** and **12** resulted exclusively in the formation of *β*-iodo-enamides **26** and **27**, respectively, in good yield and with complete *E*-double bond selectivity in both instances. Significantly, aromatic *N*-formylimides (**16**, **17**) proved inert under the reaction conditions affording only returned starting materials, whereas the same substrates generated the dibromo-enamide products in good yield. Furthermore, the steric environment surrounding the *N*-formyl group seems to influence the iodo-olefination significantly. For example, while the butyramide-derived imide **14** was diiodo-olefinated in moderate yield, the *N*-methyl analogue **15** failed to react under the same reaction conditions.

Returning to the dibromo-olefination, it bears mention that the nature and efficiency of this result are extremely unusual. Dihalo-olefins are seldom detected as side products during the olefination of ketones and aldehydes.[10] Perhaps the closest and best studied example is the dibromo-olefination of lactones reported by Chapleur and co-workers in 2001 (Figure 3).[14]

Table 2. Iodo-olefination of *N*-Formylimides



[a]All reactions were conducted using 1 equiv of *N*-formylimide, 10 equiv of phosphonium salt, and 10 equiv of base in dry THF (0.33 M) at rt for 12 h.

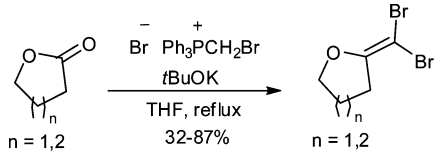
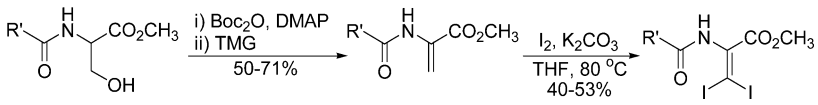


Figure 3. Chapleur's Dibromo-olefination of Lactones.

Mechanistically, the formation of the *β,β*-dibromo-enamides using (bromomethyl)triphenylphosphonium bromide could follow two potentially competing reaction pathways, as proposed by Chapleur in explaining the lactone dibromo-olefination.[14] Initially, deprotonation of the phosphonium salt

Scheme 5. Ferreira's Synthesis of *β,β*-Diiodo-enamides



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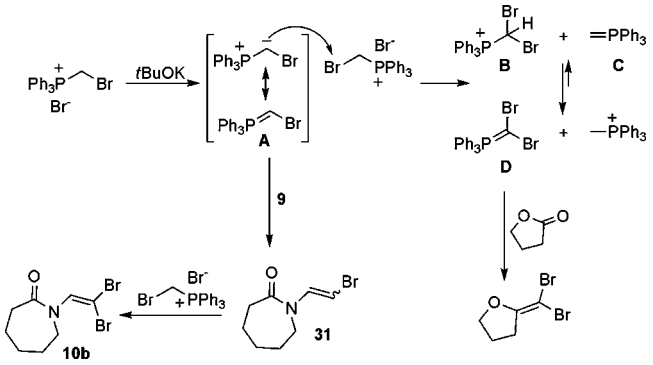
yields ylide **A**, which then reacts with a second equivalent of the phosphonium salt to generate the dibromo-phosphonium unit **B** and methylene ylide **C**. Deprotonation of the dibromo phosphonium salt by either ylide **C** or *tert*-butoxide then yields the dibromomethylenetriphenylphosphorane **D** (Scheme 6).

Scheme 6. Potential Dihalo-olefination Mechanisms



Chapleur concluded that the lactone dibromo-olefination was taking place through the formation of the dibromomethylene-triphenylphosphorane **D** that then reacted with the lactone starting material to afford the observed dibromo enol ether in a single step.

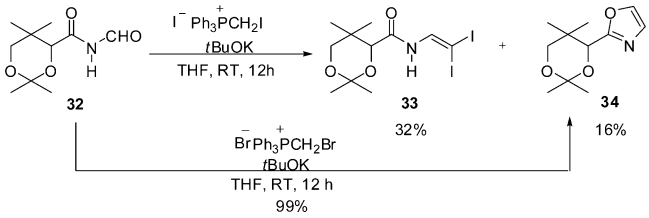
In the case of *N*-formylimides, we believe that the *N*-formylimide reacts with the bromomethylenetriphenylphosphorane **A** to yield a bromo-enamide intermediate **31**, which then undergoes a second bromination to generate the observed dibromo-enamide. Evidence for a stepwise process was provided by control experiments in which valeraldehyde generated the expected monohalogenated olefin when subjected to the same reaction conditions, demonstrating the enamide nitrogen's pivotal role during the bromination step. Further indication that a stepwise pathway is taking place was provided by the fact that none of the *N*-formylimides reacted with the dibromo ylide **D** generated through Ramirez olefination conditions.

The high isolated yield of iodo-enamides **25** and **26** supports the theory that a stepwise process is taking place and that the rate for the second halogenation step is highly dependent on the structural nature of the initial halo-enamide intermediate generated. Alternatively, it could be implied that *N*-formylimides with closely related structures have very different rates of reaction with ylides **A** or **D** and that the iodo-enamide products obtained from the reaction with ylide **A** are not intermediates on the pathway for the synthesis of diiodo-enamides.

Additional evidence for a stepwise process was provided by treatment of the pantolactone-derived *N*-formylimide **32** under the same iodo-olefination conditions. This resulted in the formation of diiodo-enamide **33** and oxazole **34** (Scheme 7). In contrast, bromo-olefination of pantolactone-derived *N*-formylimide, **32**, gave oxazole **34** in near quantitative yield. The structures of both the diiodo-enamide and oxazole were corroborated by crystallographic analysis (Figure 4).[15,16]

The oxazole is presumably generated through the intramolecular cyclization of the iodo-enamide intermediate obtained in a manner similar to that reported by Ferreira following treatment of amino acid derived β-iodo-enamides with base (Scheme 8).[13]

Scheme 7. Halo-olefination of Pantolactone-Derived *N*-Formylimide 32



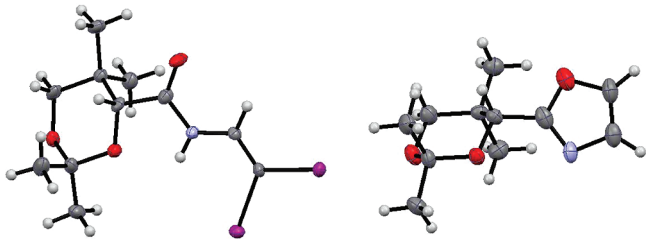


Figure 4. Crystal structures of diiodo-enamide **33** and oxazole **34**.

These results further support the theory that, at least in the case of dihalo-enamide formation, a stepwise mechanism is taking place. In any event, having successfully achieved a high-yielding, flexible, and reliable synthesis of β,β-dihalo-enamides, the key steroselective dehalogenations were attempted. We initially focused our attention on the selective dehalogenation of the diiodo-enamide units.

We are pleased to report that treatment of the diiodo-enamides with a Zn−Cu couple proceeded cleanly, generating the *E*-β-iodo-enamides **35** and **29** stereoselectively and in good yield (Table 3). Interestingly, in the case of the pantolactone-derived iodo-enamide **36**, the *Z* product was the sole isomer obtained. We believe that the opposite double bond geometry obtained in iodo-enamide **36** is the result of the electronic interactions between the tetramethyl dioxirane ring and the enamide unit affecting the reactive conformation of diiodo-enamide **33**.[7]

Having access to both the diiodo-enamide **33** and *Z*-iodo-enamide **36** provided the opportunity to further probe the mechanism of the halo-olefination taking place. It was proposed that if the stepwise mechanistic hypothesis was valid, basic treatment of iodo-enamide **36** should result in oxazole formation.

Treatment of *Z*-iodo-enamide **36** under basic conditions yielded oxazole **34** together with vinyl enamide **37**. On the other hand, treatment of diiodo-enamide **33** under identical conditions gave only unreacted starting material (Scheme 9).

These results would further support the theory that the halo-olefination of *N*-formylimides initially yields a halo-enamide intermediate, which can then either undergo a second halogenation to generate a dihalo-enamide or a deprotonation−cyclization to generate an oxazole (Scheme 10).

Having demonstrated the feasibility of carrying out selective dehalogenations on diiodo-enamides, it was left to apply the same methodology to the structurally diverse dibromo-enamides generated, with the aim of being able to access the complementary *Z*-β-bromo-enamide products.

Initial debromination attempts on dibromo-enamide **18** using the Zn−Cu couple conditions resulted in a 6:1 *E*:*Z* product ratio of β-bromo-enamides **38*E*/38*Z*** in quantitative yield (Scheme 11). Although this provides a highly efficient

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Scheme 8. Ferreira's Formation of Oxazoles from β-Iodo-enamides

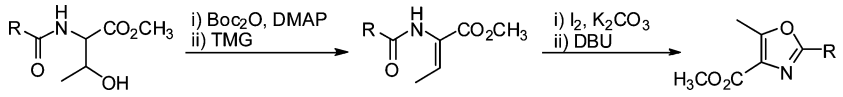
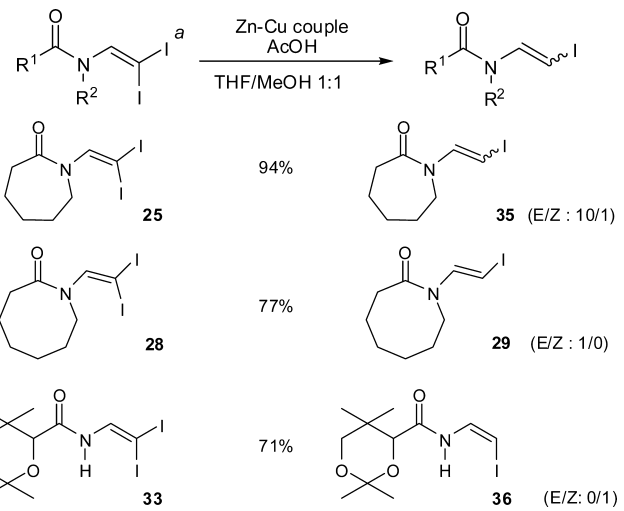
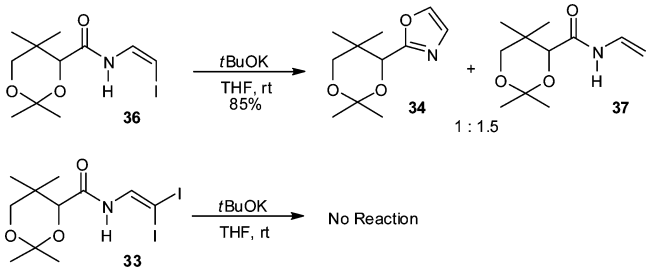


Table 3. Selective De-iodination of Diiodo-enamides

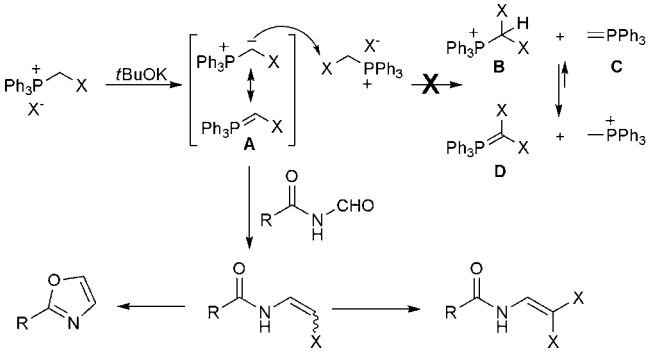


[a]All reactions were conducted using 1 equiv of diiodo-enamide, 30 equiv of Zn−Cu couple, and 100 equiv of AcOH at 0 °C for 0.5 h.

Scheme 9. Synthesis of Oxazole 34 from Iodo-enamide 36



Scheme 10. Proposed Stepwise Formation of Dihalo-enamide and Oxazole Units



approach to the synthesis of *E*-halo-enamides, it did not provide us with the complete selectivity observed in the diiodo-enamide series. However, treatment of dibromo-enamide **18** using tributyltin hydride/tetrakis(triphenylphosphine)Pd(0) afforded the highly desirable and elusive *Z*-*β*-bromo-enamide **38*Z*** in excellent yield and with complete diastereoselectivity (Scheme 11).

Faced with such unprecedented efficiency and selectivity for the synthesis of a *Z*-bromo-enamide unit, the reproducibility of the debromination conditions were assessed. We are pleased to report that, in all cases, the reduction resulted in the desired *Z*-bromo enamides **38*Z*−43** in high yields and with complete stereocontrol. Table 4 summarizes our two-step process for the efficient generation of these from the readily available *N*-formylimides (Table 4).

CONCLUSIONS

In conclusion, we have developed a flexible and stereoselective synthesis of *β*-halo-enamides taking advantage of the unprecedented and high yielding *β*,*β*-dihalo-olefination of *N*-formylimides. This effective, reproducible, and highly efficient synthesis of *β*-halo- and *β*,*β*-dihalo-enamides provides a solid protecting group-free platform from which the full potential of enamide chemistry can be realized. Furthermore, these results herein provide evidence that an alternative mechanistic pathway for dihalo-olefination to that proposed by Chapleur is likely to be taking place. We are currently carrying out further experimental and theoretical calculations to shed further light on the mechanistic aspects of this transformation.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF) and toluene were purified through a solvent purification system. Anhydrous ethyl acetate (EtOAc) and methanol (MeOH) were obtained commercially. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C unless otherwise stated. IR spectra were recorded as thin films on NaCl plates using a Fourier transform spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) and carbon magnetic resonance spectra (^{13}C NMR) were recorded respectively at 400 MHz/500 MHz and 100 MHz/125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad), (3) and coupling constant (J) quoted in hertz to the nearest 0.1 Hz. High-resolution mass spectra were recorded by electrospray (EI) or chemical ionization (CI) using a mass spectrometer operating at a

Scheme 11. Initial De-bromination Attempts

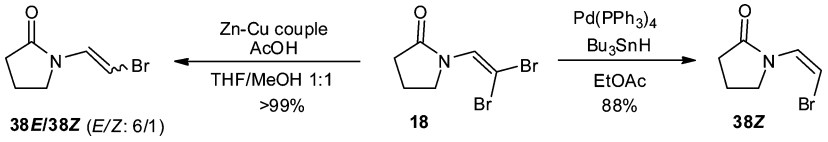


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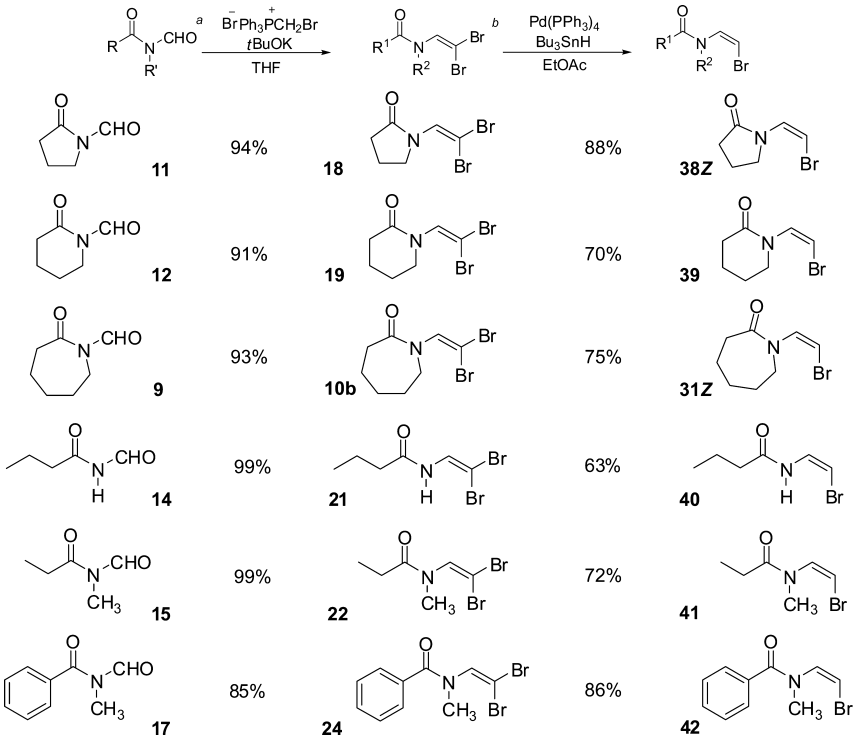
Table 4. Stereoselective Synthesis of *Z*-β-Bromo-enamides



[a]The reactions were conducted using 1 equiv of *N*-formylimide, 10 equiv of phosphonium salt, and 10 equiv of base in dry THF (0.33 M) at rt for 12 h. [b]The reactions were conducted using 1 equiv of dibromo-enamide, 1.2 equiv of Bu_3SnH, and 0.1 equiv of catalyst in dry EtOAc (16 mM) at rt for 12 h.

resolution of 15000 full widths at half height. Flash chromatography was performed using silica gel (40−63 μm) as the stationary phase. TLC was performed on aluminum sheets precoated with silica (silica gel 60 F254) unless otherwise stated where aluminum oxide plates were used. The plates were visualized by the quenching of UV fluorescence (λ_{max} 254 nm) and/or by staining with potassium permanganate followed by heating.

***N*-Formyl-*N*-methylpropionamide, 15.** A 0 °C solution of *N*-methylpropionamide (5.0 g, 57.5 mmol) in dry THF (100 mL) was treated by the dropwise addition of *n*-butyllithium (2.5 M in hexanes, 25.3 mL, 63.2 mmol). The resulting mixture was stirred at 0 °C for 1 h and then treated with a solution of *N*-formylbenzotriazole (10.15 g, 69.0 mmol) in THF (50 mL). The reaction mixture was then allowed to warm to room temperature and stirred for a further 12 h. The mixture was diluted with *t*ert-butyl methyl ether (100 mL) and quenched with satd aq $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a crude brown oil. Purification of the crude residue by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) gave 3.2 g (48%) of *N*-formylimide **15** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 9.14 (1H, s), 2.97 (3H, s), 2.56 (2H, q, J = 7.4 Hz), 1.09 (3H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.1, 162.4, 28.1, 26.3, 8.3; IR (neat) ν_{max} 2985, 1722, 1668, 1452, 1417, 1365, 1265, 1051 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 116.0707, $C_5H_{10}NO_2$ requires 116.0712.

***N*-Formyl-*N*-methylbenzamide, 17.** A 0 °C solution of *N*-methylbenzamide (5.0 g, 37 mmol) in dry THF (100 mL) was treated by the dropwise addition of *n*-butyllithium (2.5 M in hexanes, 16.3 mL, 40.7 mmol). The resulting mixture was stirred at 0 °C for 1 h and then treated with a solution of *N*-formylbenzotriazole (6.53 g, 44.4 mmol) in THF (50 mL). The reaction mixture was then allowed to warm to room temperature and stirred for a further 12 h. The mixture was diluted with *tert*-butyl methyl ether (100 mL) and quenched with satd aq $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford a crude brown oil. Purification of the crude residue by flash column chromatography (silica gel, 80:20 hexane:ethyl acetate) gave 4.8 g (81%) of *N*-formylimide **17** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 8.90 (1H, s), 7.49−7.40 (5H, m), 3.19 (3H, s); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 172.4, 164.3, 133.4, 132.0, 128.8, 128.7, 27.4; IR (neat) ν_{max} 2935, 1722, 1654, 1600, 1413, 1338, 1274, 1043, 1022 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 164.0714, $C_9H_{10}NO_2$ requires 164.0712.

(Bromomethyl)triphenylphosphonium Bromide. A solution of triphenylphosphine (60 g, 230 mmol) in dry toluene (100 mL) was treated with the dropwise addition of methylene bromide (21 mL, 300 mmol), and the resulting solution was stirred at 60 °C for 72 h. The precipitate obtained was filtered, washed with toluene (5 × 100 mL), and dried under vacuum for 12 h to yield 80.2 g (80%) of bromomethyl)triphenylphosphonium bromide as a white solid: ^{1}H NMR (400 MHz; DMSO-d_6) δ_H 7.99−7.93 (6H, m), 7.84−7.79 (3H, m), 7.73−7.68 (6H, m), 5.88 (2H, d, J = 5.4 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ_C 135.6, 135.5, 134.5, 134.4, 130.6, 130.5, 117.5, 116.6, 18.8, 18.3; IR (neat) ν_{max} 3047, 2987, 1589, 1481, 1437, 1340, 1116 cm^{-1}; HRMS (FAB+) found $(M - Br)^+$ 355.0247, $C_{19}H_{17}PBr$ requires 355.0251; mp 220 °C dec.

General Procedure A for the Dibromo-olefination of *N*-Formylimides. A suspension of (bromomethyl)-triphenylphosphonium bromide (10 equiv) in anhydrous THF was treated with potassium *tert*-butoxide (10 equiv), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 h). The resulting brown suspension was then treated dropwise with a solution of *N*-formylimide (1.0 equiv) in THF. The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 h). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers

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were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography.

1-(2,2-Dibromovinyl)azepan-2-one, 10b. Following general procedure A, (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of 2-oxoazepan-1-carbaldehyde **9** (70.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 139 mg (93%) of dibromo-enamide **10b** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.41 (1H, s), 3.66 (2H, t, J = 4.7 Hz), 2.58 (2H, t, J = 6.4 Hz), 1.84−1.80 (2H, m), 1.77−1.73 (4H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.8, 135.8, 85.2, 50.2, 37.3, 29.9, 29.4, 23.2; IR (neat) ν_{max} 3039, 2928, 1658), 1435, 1392, 1257, 1207, 1188 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 297.9261, $C_8H_{12}NOBr_2$ required 297.9265.

1-(2,2-Dibromovinyl)pyrrolidin-2-one, 18. Following general procedure A, (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of 2-oxopyrrolidine-1-carbaldehyde **11** (56.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 125 mg (94%) of dibromo-enamide **18** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.59 (1H, s), 4.01 (2H, t, J = 7.4 Hz), 2.39 (2H, t, J = 8.2 Hz), 2.09 (2H, qn, J = 7.4 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 174.7, 129.6, 74.0, 46.9, 29.9, 18.9; IR (neat) ν_{max} 3039, 2962, 2901, 1697, 1620, 1481, 1373 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 269.8957, $C_6H_8NOBr_2$ requires 269.8952.

1-(2,2-Dibromovinyl)piperidin-2-one, 19. Following general procedure A, (bromomethyl)triphenylphosphonium bromide (4.4 g, 10.0 mmol) in anhydrous THF (20 mL) was deprotonated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting ylide was treated with a solution of 2-oxopiperidine-1-carbaldehyde **12** (127 mg, 1.0 mmol) in THF (10 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 258 mg (91%) of dibromo-enamide **19** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.40 (1H, s), 3.64 (2H, t, J = 4.8 Hz), 2.45 (2H, t, J = 6.6 Hz), 1.83 (4H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 169.9, 134.8, 85.9, 48.8, 32.4, 23.1, 20.8; IR (neat) ν_{max} 3047, 2947, 1658, 1612, 1473, 1404, 1260, 1255, 1219, 1157 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 283.9102, $C_7H_{10}NOBr_2$ requires 283.9109.

1-(2,2-Dibromovinyl)azocan-2-one, 20. Following general procedure A, (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of 2-oxoazocan-1-carbaldehyde **13** (77.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane:ethyl acetate) to afford 140 mg (90%) of dibromo-enamide **20** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.42 (1H, s), 3.67 (2H, t, J = 5.1 Hz), 2.59 (2H, t, J = 6.4 Hz), 1.85−1.80 (2H, m), 1.78−1.68 (6H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.9, 135.8, 77.7, 50.2, 37.3, 29.9, 29.4, 26.3, 23.3; IR (neat) ν_{max} 3039, 2928, 1712, 1658, 1454, 1396, 1361, 1207, 1192 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 311.9413, $C_9H_{14}NOBr_2$ required 311.9422.

***N*-(2,2-Dibromovinyl)butyramide, 21.** Following general procedure A, (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of *N*-formylbutyramide **14** (57.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 140 mg (99%) of dibromo-enamide **21** as a yellow solid: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.61 (1H, d, J = 11.6 Hz), 7.13 (1H, bs), 2.27 (2H, t, J = 7.4 Hz), 1.72−1.67 (2H, m), 0.97 (3H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 169.5, 127.5, 73.7, 38.3, 18.7, 13.8; IR (neat) ν_{max} 3053, 2961, 1663, 1631, 1480, 1376, 1268, 1194 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 271.9110, $C_6H_{10}ONBr_2$ required 271.9129; mp 66 °C.

***N*-(2,2-Dibromovinyl)-*N*-methylpropionamide, 22.** Following general procedure A, (bromomethyl)triphenylphosphonium bromide (4.4 g, 10.0 mmol) in anhydrous THF (20 mL) was deprotonated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting ylide was treated with a solution of *N*-formyl-*N*-methylpropionamide **15** (115 mg, 1.0 mmol) in THF (10 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 310 mg (quant. yield) of dibromo-enamide **22** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.06 (1H, s), 3.01 (3H, s), 2.24 (2H, q, J = 7.6 Hz), 1.07 (3H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 173.0, 135.5, 94.5, 33.7, 27.8, 9.1; IR (neat) ν_{max} 2980, 2939, 1666, 1595, 1462, 1373, 1265, 1062 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 269.9130, $C_6H_{10}NOBr_2$ requires 269.9129.

***N*-(2,2-Dibromovinyl)benzamide, 23.** Following general procedure A, (bromomethyl)triphenylphosphonium bromide (4.4 g, 10.0 mmol) in anhydrous THF (20 mL) was deprotonated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting ylide was treated with a solution of *N*-formylbenzamide **16** (149 mg, 1.0 mmol) in THF (10 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane:ethyl acetate) to afford 241 mg (79%) of dibromo-enamide **23** as a yellow solid: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.85−7.82 (4H, m), 7.59 (1H, tt, J = 6.8, 1.2 Hz Hz), 7.50 (2H, tm, J = 7.6 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 163.4, 132.9, 132.5, 129.2, 127.8, 127.4, 75.0; IR (neat) ν_{max} 3396, 3066, 1660, 1629, 1504, 1467, 1249, 848 cm^{-1}; HRMS (EI+) found $(M)^+$ 304.8883, $C_9H_7NOBr_2$ requires 304.8874; mp 60 °C.

***N*-(2,2-Dibromovinyl)-*N*-methylbenzamide, 24.** Following general procedure A, (bromomethyl)triphenylphosphonium bromide (4.4 g, 10.0 mmol) in anhydrous THF (20 mL) was deprotonated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting ylide was treated with a solution of *N*-formyl-*N*-methylbenzamide **17** (163 mg, 1.0 mmol) in THF (10 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 270 mg (85%) of dibromo-enamide **24** as a yellow solid: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.52−7.47 (2H, m), 7.46−7.41 (1H, m), 7.40−7.36 (2H, m), 7.09 (1H, bs), 3.26 (3H, s); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 170.5, 136.8, 135.0, 131.0, 128.3, 128.2, 90.0, 34.9; IR (neat) ν_{max} 3020, 2933, 1716, 1647, 1597, 1346, 1323 cm^{-1}; HRMS (CI+) found $(M)^+$ 316.9045, $C_{10}H_9NOBr_2$ requires 316.9051; mp 80 °C.

2-(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)oxazole, 34. Following general procedure A, (bromomethyl)triphenylphosphonium bromide (2.2 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of *N*-formyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **32** (107.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane:ethyl acetate) to afford 105 mg (99%) of oxazole **34** as a yellow solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.64 (1H, s), 7.09 (1H, s), 4.90 (1H, s), 3.78 (1H, d, J = 11.4 Hz), 3.41 (1H, d, J = 11.4 Hz), 1.53 (3H, s), 1.50 (3H, s), 1.06 (3H, s), 0.86 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 161.2, 138.9, 127.0, 99.7, 74.8, 71.6, 34.2, 29.5, 21.8, 19.3, 18.7; IR (neat) ν_{max} 3119, 2994, 2969, 1574, 1523, 1459, 1392, 1383, 1370, 1193, 1157 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 212.1282, $C_{11}H_{18}NO_3$ requires 212.1287; mp 68−70 °C.

(Iodomethyl)triphenylphosphonium Iodide. A solution of triphenylphosphine (30 g, 114.4 mmol) in dry toluene (50 mL) was treated dropwise with methylene iodide (12 mL, 148.9 mmol). The reaction mixture was allowed to stir at 60 °C for 72 h, which caused a white precipitate to form. The suspension was then cooled down to room temperature, filtered and the white solid residue was washed several times with toluene (5 × 200 mL). The crude product was dried under vacuum for 12 h to afford 55 g (91%) of the phosphonium iodide as a pure white solid: ^{1}H NMR (400 MHz; DMSO-d_6) δ_H 7.98−7.81 (15H, m), 5.10 (2H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ_C 136.1, 136.0, 134.8, 134.7, 131.2, 131.0, 119.7, 118.8, −14.9, −15.4; IR (neat) ν_{max} 2994, 2970, 1575, 1459, 1392, 1383 cm^{-1}; HRMS (FAB+) found $(M - I)^+$ 403.0110, $C_{19}H_{17}PI$ requires 403.0113; mp 235 °C.

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General Procedure B for the Diiodo-olefination of *N*-Formylimides. A suspension of (iodomethyl)triphenylphosphonium iodide (10 equiv) in anhydrous THF was treated with potassium *tert*-butoxide (10 equiv), and the resulting bright orange suspension was allowed to stir at room temperature until it turned brown, indicating the ylide formation (6 h). The resulting brown suspension was then treated dropwise with a solution of *N*-formylimide (1.0 equiv) in THF. The resulting mixture was stirred at room temperature until TLC analysis showed reaction completion (12 h). The reaction mixture was quenched with distilled water (10 mL) and poured into hexanes (25 mL), and the precipitate formed was filtered off. The phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum, and the crude residue was purified by flash column chromatography.

1-(2,2-Diiodovinyl)azepan-2-one, 25. Following general procedure B, (iodomethyl)triphenylphosphonium iodide (5.30 g, 10.0 mmol) in anhydrous THF (20 mL) was deprotonated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting ylide was treated with a solution of 2-oxoazepane-1-carbaldehyde **9** (141.2 mg, 1.0 mmol) in THF (10 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane:ethyl acetate) to afford 390 mg (99%) of diiodo-enamide **25** as a yellow solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.73 (1H, s), 3.64 (2H, t, J = 4.4 Hz), 2.58−2.55 (2H, m), 1.83−1.74 (6H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 175.4, 147.3, 50.6, 37.4, 31.7, 29.9, 22.8, 14.2; IR (neat) ν_{max} 3010, 2930, 2910, 1646, 1587, 1464., 1443, cm^{-1}; HRMS (CI+) found (M + H)$^+$ 391.9003, $C_8H_{12}NOI_2$ requires 391.9008; mp 75 °C.

(*E*)-1-(2-Iodovinyl)pyrrolidin-2-one, 26. Following general procedure B, (iodomethyl)triphenylphosphonium iodide (2.65 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of 2-oxopyrrolidin-1-carbaldehyde **11** (56.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 92 mg (78%) of iodo-enamide **26** as a yellow solid: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.59 (1H, d, J = 15.0 Hz), 5.37 (1H, d, J = 15.0 Hz), 3.51 (2H, t, J = 7.1 Hz), 2.46 (2H, t, J = 7.8 Hz), 2.12 (2H, qn, J = 7.5 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 172.3, 134.7, 55.0, 44.6, 30.6, 17.4; IR (neat) ν_{max} 3057, 2957, 2917, 2889, 1685, 1607, 1480, 1457, 1263, 1174 cm^{-1}; HRMS (EI) found (M)$^+$ 236.9651, C_6H_8NOI requires 236.9655; mp 28 °C.

(*E*)-1-(2-Iodovinyl)piperidin-2-one, 27. Following general procedure B, (iodomethyl)triphenylphosphonium iodide (2.65 g, 5.0 mmol) in anhydrous THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.6 g, 5.0 mmol), and the resulting ylide was treated with a solution of 2-oxopiperidin-1-carbaldehyde **12** (63.5 mg,0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 100 mg (80%) of iodo-enamide **27** as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, J = 14.0 Hz), 5.44 (1H, d, J = 14.0 Hz), 3.41 (2H, t, J = 6.0 Hz), 2.48 (2H, t, J = 6.4 Hz), 1.88−1.81 (2H, m), 1.79−1.70 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 137.7, 55.0, 45.0, 32.8, 22.4, 20.6; IR (neat) ν_{max} 2924, 2854, 1651, 1599, 1458, 1404, 1296, 1257 cm^{-1}; HRMS (CI/ISO) found (M + H)$^+$ 251.9885, $C_7H_{11}NOI$ requires 251.9886; mp 33 °C.

1-(2,2-Diiodovinyl)azocan-2-one, 28, and (*E*)-1-(2-Iodovinyl)-azocan-2-one, 29. Following general procedure B, (iodomethyl)-triphenylphosphonium iodide (5.30 g, 10.0 mmol) in anhydrous THF (20 mL) was deprotonated with potassium *tert*-butoxide (1.12 g, 10.0 mmol), and the resulting ylide was treated with a solution of 2-oxoazocane-1-carbaldehyde **13** (155 mg, 1.0 mmol) in THF (10 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexanes: ethyl acetate) to yield 386 mg of an inseparable 13:1 mixture of diiodo-enamide **28** (89%) and *E*-iodo-enamide **29** (10%).

1-(2,2-Diiodovinyl)azocan-2-one, 28: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.56 (1H, s), 3.78 (2H, t, J = 5.6 Hz), 2.53 (2H, t, J = 6.3 Hz), 1.88−1.82 (2H, m), 1.69−1.58 (4H, m), 1.53−1.47 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 175.6, 145.2, 47.0, 34.3, 30.1, 28.8, 26.3, 24.3, 13.1; IR (neat) ν_{max} 2916, 2852, 1628, 1617, 1588, 1472, 1444 cm^{-1}; HRMS (CI+) found (M + H)$^+$ 405.9169, $C_9H_{14}NOI_2$ requires 405.9165. (*E*)-1-(2-Iodovinyl)azocan-2-one, **29**: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.95 (1H, d, J = 14.0 Hz), 5.52 (1H, d, J = 14.0 Hz).

***N*-(2,2-Diiodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, 33, and 2-(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)-oxazole, 34.** Following general procedure B, (iodomethyl)-triphenylphosphonium iodide (1.20 g, 2.25 mmol) in dry THF (10 mL) was deprotonated with potassium *tert*-butoxide (0.252 g, 2.25 mmol mmol) and the resulting ylide was treated with a solution of *N*-formyl-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **32** (107.5 mg, 0.5 mmol) in THF (5 mL). The crude brown oil was purified by flash column chromatography (silica gel, 80:20 hexanes: ethyl acetate) to yield 74 mg (32%) of diiodo-enamide **33** and 17 mg (16%) of oxazole **34** as yellow solids.

***N*-(2,2-Diiodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, 33:** ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 8.34 (1H, bd, J = 10.8 Hz), 7.76 (1H, d, J = 11.4 Hz), 4.14 (1H, s), 3.71 (1H, d, J = 11.7 Hz), 3.32 (1H, d, J = 11.7 Hz), 1.51 (3H, s), 1.45 (3H, s), 1.03 (3H, s), 1.02 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 166.1, 136.4, 99.4, 77.1, 71.4, 33.3, 29.5, 22.9, 18.8,19.1, −6.8; IR (neat) ν_{max} 3351, 2836, 1686, 1612, 1465, 1384, 1379, 1094, 1050 cm^{-1}; HRMS (CI+) found (M + H)$^+$ 465.9372, $C_{11}H_{18}NO_3I_2$ requires 465.9376; mp 135 °C.

2-(2,2,5,5-Tetramethyl-1,3-dioxan-4-yl)oxazole, 34: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.64 (1H, s), 7.09 (1H, s), 4.90 (1H, s), 3.78 (1H, d, J = 11.4 Hz), 3.41 (1H, d, J = 11.4 Hz), 1.53 (3H, s), 1.50 (3H, s), 1.06 (3H, s), 0.86 (3H, s).

General Procedure C for the Dehalogenation of Dihaloenamides. The dihaloenamide (1 equiv) was dissolved in an anhydrous MeOH/THF mixture (1:1), and the resulting solution was cooled to 0 °C. The solution was treated with Zn−Cu couple (30 equiv) and glacial acetic acid (100 equiv), and the resulting reaction mixture was stirred at 0 °C until completion by TLC analysis (30 min). The reaction was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum.

(*E*)-1-(2-Iodovinyl)azepan-2-one, 35*E*, and (*Z*)-1-(2-Iodovinyl)azepan-2-one, 35*Z*. Following general procedure C, 1-(2,2-diiodovinyl)azepan-2-one **25** (380 mg, 0.97 mmol) was dissolved in anhydrous MeOH/THF (1:1, 20 mL total volume) and treated with Zn−Cu couple (3.7 g, 29.1 mmol) and glacial acetic acid (5.9 mL, 97.0 mmol) to yield 240 mg (94%) of iodo enamides **35*E*** and **35*Z*** (10:1 ratio) as an inseparable mixture. (*E*)-1-(2-Iodovinyl)azepan-2-one, **35*E***: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.84 (1H, d, J = 13.7 Hz), 5.51 (1H, d, J = 14.2 Hz), 3.57−3.52 (2H, m), 2.63−2.58 (2H, m), 1.75−1.67 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.5, 137.3, 55.0, 45.1, 36.9, 29.4, 27.5, 23.4. (*Z*)-1-(2-Iodovinyl)azepan-2-one, **35*Z***: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.45 (1H, d, J = 6.3 Hz), 5.83 (1H, d, J = 6.9 Hz), 3.76−3.73 (2H, m), 2.63−2.58 (2H, m), 1.75−1.67 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 138.6, 66.9,49.5, 37.4, 30.4, 29.8, 23.3; IR (neat) ν_{max} 2930, 1658, 1602, 1476, 1389, 1325, 1191 cm^{-1}; HRMS (CI/ISO) found (M + H)$^+$ 266.0042, $C_8H_{13}NOI$ requires 266.0041.

(*E*)-1-(2-Iodovinyl)azocan-2-one, 29. Following general procedure C, 1-(2,2-diiodovinyl)azocan-2-one **28** (405 mg, 1.0 mmol) was dissolved in anhydrous MeOH/THF (20 mL total volume) and treated with Zn−Cu couple (3.81 g, 30.0 mmol) and glacial acetic acid (6.1 mL, 100.0 mmol) to yield 215 mg (77%) of iodo enamide **29** as white solid which did not require any further purification: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.90 (1H, d, J = 13.7 Hz), 5.52 (1H, d, J = 13.6 Hz), 3.75−3.69 (2H,m), 2.61−2.56 (2H, m), 1.88−1.80 (2H, m), 1.74−1.66 (2H, m), 1.60−1.52 (2H, m), 1.50−1.42 (2H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 172.9, 136.1, 55.6, 43.6, 34.3, 29.1, 27.8, 26.3, 24.1; IR (neat) ν_{max} 3083, 2938, 2929, 2915, 1647, 1603, 1484, 1453, 1388, 1312 cm^{-1}; HRMS (CI/ISO) found (M + H)$^+$ 280.0198, $C_9H_{15}NOI$ requires 280.0203; mp 54 °C.

***(Z)*-*N*-(2-Iodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide, 36.** Following general procedure C, *N*-(2,2-diiodovinyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carboxamide **33** (160 mg, 0.344 mmol) was dissolved in anhydrous MeOH/THF mixture (10 mL

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total volume) and was treated with Zn−Cu couple (1.33 g, 10.32 mmol) and glacial acetic acid (2.1 mL, 34.4 mmol) to yield 80 mg (71%) of iodo enamide **36** as a yellow solid, which did not require any further purification: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 8.90−8.77 (1H, m), 7.57 (1H, dd, J = 11.3, 6.5 Hz), 5.72 (1H, d, J = 6.4 Hz), 4.46 (1H, s), 4.01 (1H, d, J = 11.5 Hz), 3.61 (1H, d, J = 11.5 Hz), 1.83 (3H, s), 1.76 (3H, s), 1.34 (3H, s), 1.33 (3H, s); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 167.5, 129.3, 99.3, 77.2, 71.4, 61.3, 33.2, 29.5, 21.9, 19.0, 18.0; IR (neat) ν_{max} 2988, 2956, 2872, 1699, 1626, 1464, 1375, 1285, 1235 cm^{-1}; HRMS (EI) found $(M)^+$ 339.0332, $C_{11}H_{18}NO_3I$ requires 339.0331; mp 110 °C.

General Procedure D for the Dehalogenation of Dihaloenamides. A solution of dihaloenamide (1 equiv) in anhydrous EtOAc (5 mL) was treated with $Pd(PPh_3)_4$ (0.1 equiv) and Bu_3SnH (1.2 equiv). The resulting reaction mixture was stirred at room temperature until completion as indicated by TLC analysis (12 h). The reaction was diluted with hexane (15 mL), filtered through Celite, and concentrated under vacuum to afford a crude residue which was purified by flash column chromatography.

(*Z*)-1-(2-Bromovinyl)pyrrolidin-2-one, 38. Following general procedure D, a solution of 1-(2,2-dibromovinyl)pyrrolidin-2-one **18** (90 mg, 0.34 mmol) in anhydrous EtOAc (5 mL) was treated with $Pd(PPh_3)_4$ (39 mg, 0.03 mmol) and Bu_3SnH (0.11 mL, 0.40 mmol). The crude yellow oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 56 mg (88%) of bromo-enamide **38** as a colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.29 (1H, d, J = 7.0 Hz), 5.41 (1H, d, J = 7.0 Hz), 4.14 (2H, t, J = 7.2 Hz), 2.41 (2H, t, J = 7.8 Hz), 2.09 (2H, qn, J = 7.4 Hz); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 175.3, 126.2, 86.6, 47.5, 30.1, 18.8; IR (neat) ν_{max} 2953, 1703, 1640, 1484, 1381, 1313, 1251 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 189.9865, C_6H_9NOBr requires 189.9868.

(*Z*)-1-(2-Bromovinyl)piperidin-2-one, 39. Following general procedure D, a solution of 1-(2,2-dibromovinyl)piperidin-2-one **19** (169 mg, 0.60 mmol) in anhydrous EtOAc (32 mL) was treated with $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) and Bu_3SnH (0.2 mL, 0.71 mmol). The crude yellow oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 86 mg (70%) of bromo-enamide **39** as a colorless oil: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.37 (1H, d, J = 6.5 Hz), 5.74 (1H, d, J = 6.5 Hz), 3.83−3.78 (2H, m), 2.51−2.46 (2H, m), 1.89−1.79 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 170.3, 131.6, 94.8, 48.9, 32.4, 23.1, 20.8; IR (neat) ν_{max} 2953, 2877, 1656, 1626, 1477, 1460, 1427, 1406, 1269, 1172 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 204.0026, $C_7H_{11}NOBr$ requires 204.0024.

(*Z*)-1-(2-Bromovinyl)azepan-2-one, 31*Z*. Following general procedure D, a solution of 1-(2,2-dibromovinyl)azepan-2-one **10b** (118 mg, 0.40 mmol) in anhydrous EtOAc (30 mL) was treated with $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) and Bu_3SnH (0.13 mL, 0.48 mmol). The crude yellow oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 65 mg (75%) of bromo-enamide **31*Z*** as a colorless oil: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.29 (1H, d, J = 6.3 Hz), 5.73 (1H, d, J = 6.3 Hz), 3.80−3.76 (2H, m), 2.63−2.61 (2H, m), 1.90−1.81 (2H, m), 1.79−1.71 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 176.4, 132.6, 94.8, 49.4, 37.3, 29.9, 29.3, 23.4; IR (neat) ν_{max} 2929, 2856, 1739, 1666, 1627, 1394, 1332, 1321, 1190 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 218.0181, $C_8H_{13}NOBr$ requires 218.0181.

(*Z*)-*N*-(2-Bromovinyl)butyramide, 40 and 2-Propyloxazole. Following general procedure D, a solution of *N*-(2,2-dibromovinyl)-butyramide **21** (63 mg, 0.23 mmol) in anhydrous EtOAc (3 mL) was treated with $Pd(PPh_3)_4$ (27 mg, 0.02 mmol) and Bu_3SnH (0.10 mL, 0.28 mmol). The crude yellow oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 28 mg (63%) of bromo-enamide **40** and 9.6 mg (37%) of 2-propyl-oxazole as colorless oils.

(*Z*)-*N*-(2-Bromovinyl)butyramide, 40: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.40 (1H, dd, J = 10.9, 5.9 Hz), 7.32 (1H, bs), 5.47 (1H, d, J = 5.3 Hz), 2.30 (2H, t, J = 7.3 Hz), 1.71 (2H, sextet, J = 7.4 Hz), 0.99 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 169.5, 127.5, 88.3, 38.4, 18.8, 13.8; HRMS (CI+) found $(M + H)^+$ 192.0018, $C_6H_{11}NOBr$ requires 192.0024; IR (neat) ν_{max} 2961, 1677, 1642, 1239, 1195, 678 cm^{-1}.

2-Propyloxazole: ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.63 (1 H, d, J = 10.9 Hz), 7.08 (1 H, bs), 2.28 (2H, t, J = 7.6 Hz), 1.72 (2H, sextet, J = 7.4 Hz), 0.98 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 131.0, 128.9, 125.4, 29.1, 23.1, 11.1; HRMS (CI+) found $(M + H)^+$ 112.0769, $C_6H_{10}NO$ requires 112.0762; IR (neat) ν_{max} 2961, 1677, 1642, 1239, 1195, 678 cm^{-1}.

(*Z*)-*N*-(2-Bromovinyl)-*N*-methylpropionamide, 41. Following general procedure D, a solution of *N*-(2,2-dibromovinyl)-*N*-methyl-propionamide **22** (117 mg, 0.43 mmol) in anhydrous EtOAc (10 mL) was treated with $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) and Bu_3SnH (0.14 mL, 0.52 mmol). The crude yellow oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethylacetate) to afford 60 mg (72%) of bromo-enamide **41** as a colorless oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 6.95 (1H, bs), 6.00 (1H, bs), 3.16 (3H, s), 2.31−2.30 (2H, m), 1.15−1.12 (3H, m); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 173.6, 133.3, 102.3, 34.0, 27.8, 9.2; IR (neat) ν_{max} 3086, 3063, 2920, 1654, 1624, 1577, 1446, 1346, 1300, 1057 cm^{-1}; HRMS (CI+) found $(M)^+$ 192.0015, $C_6H_{11}NOBr$ requires 192.0024.

(*Z*)-*N*-(2-Bromovinyl)-*N*-methylbenzamide, 42. Following general procedure D, a solution of *N*-(2,2-dibromovinyl)-*N*-methylbenzamide **24** (98 mg, 0.31 mmol) in anhydrous EtOAc (5 mL) was treated with $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) and Bu_3SnH (0.1 mL, 0.37 mmol). The crude yellow oil was purified by flash column chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford 63 mg (86%) of bromo-enamide **42** as a yellow oil: ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.51−7.49 (2H, m), 7.46−7.43 (1H, m), 7.39−7.37 (2H, m), 6.96 (1H, bs), 5.73 (1H, d, J = 6.0 Hz), 3.40 (3H, s); ^{13}C NMR (125 MHz; $CDCl_3$) δ_C 171.4, 135.4, 134.6, 130.9, 128.4, 97.3, 35.2, 29.8; IR (neat) ν_{max} 3086, 2982, 1666, 1631, 1612, 1462, 1423, 1377, 1276, 1057 cm^{-1}; HRMS (CI+) found $(M + H)^+$ 240.0026, $C_{10}H_{11}NOBr$ requires 240.0024.

Crystallographic Data Collection and Refinement Details. X-ray diffraction data of crystals of **25**, **33**, and **34** were collected at 150 K on an Oxford Diffraction Gemini A Ultra diffractometer equipped with an Oxford Cryosystems Cryostream low-temperature device, a graphite-monochromated Enhance Ultra Mo Kα radiation (λ = 0.71073 Å) source and an Atlas CCD detector. Data reduction was carried out and an analytical numeric absorption correction applied (based on expressions derived in Clark, R. C.; Reid, J. S. *Acta Crystallogr.* **1995**, *A51*, 887−897) using CrysAlisPro software (Oxford Diffraction Ltd, Version 1.171.33.55, Oxfordshire, UK). The structures were all solved by direct methods using the program SHELXS97 (SHELX, Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112−122) and refined using full-matrix least-squares refinement on F^2 (SHELX Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112−122) within the WinGX program suite (Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837−838). Full refinement details are given in the Supporting Information and the CIF. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC833481, 833478, and 833480), and copies of these data can be obtained free of charge via www. ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data of the described compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Michael E. Jung on the occasion of his 65th birthday.

■ REFERENCES

(1) (a) McAlonan, H.; Murphy, J. P.; Nieuwhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69. (b) Shirokawa, S. I.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosowaka, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604.

(2) (a) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373. (b) Overman, L. E.; Freerks, R. L. *J. Org. Chem.* **1981**, *46*, 2833. (c) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (d) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843.

(3) (a) Vidal, J. P.; Escale, R.; Girard, J. P.; Rossi, J. C.; Chantraine, J. M.; Aumelas, A. *J. Org. Chem.* **1992**, *57*, 5857. (b) Sugie, Y.; Dekker, K. A.; Hirai, H.; Ichiba, T.; Ishiguro, M.; Shiomi, Y.; Sugiura, A.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, Y. *J. Antibiot.* **2001**, *54*, 1060. (c) Kunze, B.; Jansen, R.; Hoefle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881. (d) Diyabalange, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630. (e) Patel, P. S.; Huang, S.; Fisher, S.; Pirnik, D.; Aklonis, C.; Dean, L.; Meyers, E.; Fernandes, P.; Mayerl, F. *J. Antibiot.* **1995**, *48*, 997. (f) Butcher, R. A.; Schroeder, F. C.; Fischbach, M. A.; Straight, P. D.; Kolter, R.; Walsh, C. T.; Clardy, J. *Proc. Nat. Acad. U.S.A.* **2007**, *104*, 1506. (g) Shimasaki, H.; Kagechika, H.; Fukasawa, H.; Kawachi, E.; Shudo, K. *Chem. Pharm. Bull.* **1995**, *43*, 100.

(4) For excellent reviews on the synthesis of enamides and dienamides, see: (a) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag: Stuttgart, 2005; Chapter 21.4. (b) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455.

(5) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905.

(6) (a) Boiko, V. I.; Sinitsa, A. A.; Onys'ko, P. P. *Russ. J. Gen. Chem.* **1999**, *69*, 1879. (b) Meier, S.; Werthwein, E. U. *Chem. Ber.* **1990**, *123*, 2339. (c) Kondrat'eva, G. Y.; Agafonov, N. E.; Stashina, G. A. *IzV. Akad. Nauk, Ser. Khim.* **1989**, *9*, 1873. (d) Ivanov, C.; Dobrev, A.; Nechev, L.; Nikiforov, T. *Synth. Commun.* **1989**, *19*, 297. (e) Mironova, D. F.; Loginova, N. A. *Ukr. Khim. Zh.* **1986**, *52*, 71. (f) Del'tsova, D. P.; Zeifman, Y. V.; Gambaryan, N. P. *IzV. Akad. Nauk, Ser. Khim.* **1985**, *11*, 2345.

(7) (a) Bal'on, Y. G.; Moskaleva, R. N. *Zh. Org. Khim.* **1983**, *19*, 2456. (b) Bal'on, Y. G.; Moskaleva, R. N. *Zh. Org. Khim.* **1978**, *14*, 147. (c) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak., C. A. *Org. Lett.* **2003**, *5*, 1547. (d) Smith, A. B. III; Duffey, M. O.; Basu, K.; Walsh, S. P.; Suennemann, H. W.; Frohn, M. *J. Am. Chem. Soc.* **2008**, *130*, 422. (e) Sanapo, G. F.; Daoust, B. *Tetrahedron Lett.* **2008**, *49*, 4196. (f) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (g) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (h) Pasqua, A. E.; Thomas, L. H.; Crawford, J. J.; Marquez, R. *Tetrahedron* **2011**, *67*, 7611.

(8) (a) Villa, M. J. V.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G; Marquez, R. *Org. Lett.* **2007**, *9*, 1631. (b) Mathieson, J. E.; Crawford, J. J.; Schmidtmann, M.; Marquez, R. *Org. Biomol. Chem.* **2009**, *7*, 2170.

(9) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.

(10) (a) Brückner, D. *Synlett* **2000**, 1402. (b) Brückner, D. *Tetrahedron* **2006**, *62*, 3809.

(11) Chai, D. I.; Hoffmeister, L.; Lautens, M. *Org. Lett.* **2011**, *13*, 106.

(12) The atomic coordinates for **25** (CCDC deposition no. CCDC833481) are available upon request from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom. The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.

(13) (a) Ferreira, P. M. T.; Monteiro, L. S.; Pereira, G. *Amino acids* **2010**, *39*, 499. (b) Ferreira, P. M. T.; Monteiro, L. S.; Pereira, G. *Eur. J. Org. Chem.* **2008**, 4676.

(14) Lakhrissi, Y.; Taillefumier, C.; Chretien, F.; Chapleur, Y. *Tetrahedron Lett.* **2001**, *42*, 7265.

(15) The atomic coordinates for **33** (CCDC deposition no. CCDC833478) are available upon request from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom. The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.

(16) The atomic coordinates for **34** (CCDC deposition no. CCDC833480) are available upon request from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom. The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.