DIRECT SYNTHESIS OF 4-ACETYL-1-ALKYL-1H-PYRROL-2(5H)-ONES FROM DIFUNCTIONALIZED ALLYL BROMIDE

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Abstract We describe a simple and efficient protocol for accessing some unsaturated heterocyclic compounds in a direct evaluation of allyl bromide as Z-ethyl 3-bromomethyl-4-oxopent-2-enoate. The latter reacts with primary amines via two successive nucleophilic substitutions followed by a 5-exo-trig cyclization to produce selectively 4-acetyl-1-alkyl-1H-pyrrol-2(5H)-ones in good yields.

Keywords 5-Exo-trig cyclization; primary amines; pyrrol-2(5H)-ones; Z-ethyl 3-bromomethyl-4-oxopent-2-enoate

INTRODUCTION

The γ-lactam framework is an important subunit widely found in many classes of organic aza-heterocycles. They are ubiquitous structural models in various natural products and biologically active pharmaceutical compounds. A number of α,β-unsaturated γ-lactams have been shown to exhibit significant pharmacological activities and are considered as important synthons[1] especially for the preparation of γ-amino acids,[2] various alkaloids,[3] and natural products.[4] It is also known that some of these five-membered ring compounds develop antitumor properties,[5] as well as inhibit COX-2[6] and HIV protease,[7] and hence their potential applications have stimulated much interest in the construction of these kinds of molecules.[8]
Some general methods have been developed to access these five-membered heterocycles through the condensation of dimethoxydihydrofuran derivatives with primary amines,[9] the cyclization reaction of γ-stannylated allylic aminoester,[10] the addition of primary amines to difunctionalized symmetrical 1,3-dienes[11] or to dimethyl α-(bromomethyl) fumarate,[12] acidic treatments of β-methoxy-α-aminoesters,[13] heating methanolsulfonyl γ-lactam derivatives,[14] the Horner–Wadsworth–Emmons (HWE) reaction of phosphono-γ-lactams,[15] the one-pot, three-component condensation of acylpyruvates, aromatic aldehydes, and ethylenediamine,[16] and reaction of rhodium(I) carbenes with alkynes and alkenes.[17] Here, we report a recent synthetic approach to 4-acetylpyrrol-2(5H)-ones 4 which, to our knowledge, has not been previously described.

RESULTS AND DISCUSSION

According to the procedure developed earlier by our group,[18] commercial acetylacetone was successfully converted into ethyl 3-acetyl-4-oxopentanoate 1 using NaH in dry tetrahydrofuran (THF) and ethyl bromoacetate at reflux. The second step consisted of the decylation of 2-alkylated-2,4-diketone using 30% aqueous formaldehyde and concentrated (6–10 M) solution of potassium carbonate, which afforded the vinyl ketone 2 (Scheme 1).

α-Bromomethylated substrates are recognized as being of great importance. During recent years, reports have shown the value of allyl bromides as powerful reagents in the synthesis of β-functional α-methylene-γ-butyrolactones,[19] retinoic acids,[20] and cyclic ketones,[21] in the substitution reaction with enamines,[22] and sulfite salts,[23] in oxidation with dimethylsulfoxide (DMSO),[24] and in the cycloaddition reaction of the corresponding pyridinium ylides.[25] For these reasons, a great deal of effort has been devoted to the development of methods for the preparation of compounds bearing α-bromomethyl moieties. However, only one method has been reported[26] for the preparation of the α-bromomethylated ketoester 4 using N-bromosuccinimide (NBS) as the brominating agent. On the other hand, we have shown that the addition of dibromine in carbon tetrachloride at room temperature to the vinyl ketone 2 followed by an efficient regio- and stereoselective dehydrobromination[27] of the dibrominated adduct 3 using triethylamine at 0°C produced ethyl 3-bromomethyl-4-oxopent-2-enoate 4 in 74% yield. The interpretation of the nuclear Overhauser effect spectroscopy (NOESY) 1H NMR spectra led to the assignment of its configuration. The absence of correlation between the CH2Br protons and the ethylenic proton CH was in favor of the Z-configuration (Scheme 2).

Because the γ-lactams are very interesting compounds in terms of pharmaceutical applications, we found that allylbromide 4 readily reacted with primary amines to provide pyrrol-2(5H)-ones 5a–h arising from two consecutive bimolecular
S_{N2}'-type reactions.\textsuperscript{[28]} The first equivalent of primary amine furnished an ammonium intermediate, whereas the second equivalent allowed the isomerization of the latter, which after a 5-exo-trig intramolecular cyclization leads to the formation of pyrrol-2(5H)-ones 5a–h (Scheme 3, Table 1).

**EXPERIMENTAL**

Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were standard-grade commercial products and were used without further purification. All reactions were monitored by TLC on silica-gel plates (Fluka Kieselgel 60 F254, Merck) and the series visualized by a 254-nm ultraviolet lamp and aqueous potassium permanganate solution. Crude products were purified using column chromatography on silica gel (Fluka Kieselgel 70–230 mesh). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 MHz for \textsuperscript{1}H, 282 MHz for \textsuperscript{19}F, and 75 MHz for \textsuperscript{13}C in CDCl\textsubscript{3} as solvent and TMS as the internal standard. The chemical shifts (\(\delta\)) and coupling constants (\(J\)) are expressed in parts per million (ppm) and Hertz (Hz), respectively. All NMR spectra were acquired at room temperature. Multiplicity of peaks is indicated as s, singlet; d, doublet; t, triplet; q, quartet; qt, quintuplet; sept, septuplet; and m, multiplet. High-resolution mass spectrometry (HRMS) analyses were performed in Laberca, a laboratory at Oniris (Nantes-Atlantic National College of Veterinary Medicine, Food Science, and Engineering) on a mass spectrometer equipped with a door coupled to a linear Orbitrap (LTQ-Orbitrap of Thermo Fisher Scientific) in positive electrospray ionization.
Table 1. Synthesis of 4-acetyl-1-alkyl-1H-pyrrol-2(5H)-ones 5a–h

| Entry | R               | Time (h) | Pyrrol-2(5H)-ones 5a–h | Yield\(^a\) (%) |
|-------|-----------------|----------|------------------------|-----------------|
| 1     | PhCH\(_2\)      | 1        | ![5a](image)           | 52              |
| 2     | \(p\)-FC\(_6\)H\(_4\)CH\(_2\) | 1        | ![5b](image)           | 49              |
| 3     | \(p\)-ClC\(_6\)H\(_4\)CH\(_2\) | 0.5      | ![5c](image)           | 48              |
| 4     | PhCH\(_2\)CH\(_2\) | 0.5      | ![5d](image)           | 45              |
| 5     | ![5e](image)    | 2        |                        | 71              |
| 6     | ![5f](image)    | 2.5      |                        | 56              |
| 7     | \('Pr\)         | 1        | ![5g](image)           | 71              |
| 8     | ![5h](image)    | 1        |                        | 90              |

\(^a\)Isolated yield after purification by column chromatography.
Synthesis of Z-Ethyl 3-Bromomethyl-4-oxopent-2-enoate 4

According to previous works, ethyl 3-methylene-4-oxopentanoate 2 was obtained in 66% yield. To a stirred solution of 2 (32 mmol, 5 g) in CCl₄ (80 mL), 1.2 equiv. of bromine (38.4 mmol, 2 mL) was added dropwise at 0°C. The resulting mixture was left for 1 h at room temperature, washed with an aqueous solution of Na₂S₂O₃, and dried over MgSO₄ to eliminate excess of bromine. Triethylamine (Et₃N, 70.4 mmol, 9.6 mL) was added to the cold mixture (0°C) and stirring was continued for 3 h at room temperature. The mixture was filtered and then concentrated under reduced pressure to leave an oil, which was purified by chromatography on silica gel (petroleum ether/AcOEt, 9:1). Yield (5.52 g, 74%) as a yellow liquid; IR (KBr): νmax 2983.99, 1717.67, 1652.75, 1558.39, 1026.41, 667.94 cm⁻¹; ¹H NMR (300.13 MHz, CDCl₃): 6.60 (s, 1H, =C₆H), 4.68 (s, 2H, C₆H₂Br), 4.30 (q, 2H, 3JHH = 6.00 Hz, C₆H₂CH₃), 2.45 (s, 3H, COC₆H₃), 1.35 (t, 3H, 3JHH = 6.00 Hz, CH₂C₆H₃); ¹³C NMR (75 MHz, CDCl₃): 197.1 (C=O), 164.9 (C=O₂Et), 148.9 (=C), 128.0 (C₆H), 126.4 (CH₂=CH₃), 21.2 (CH₃CO), 14.1 (CH₃CH₂). HRMS calculated for [M+Na]⁺ C₈H₁₁O₃BrNa: 256.97838, found: 256.97842.

General Procedure for the Synthesis of 4-Acetyl-1-alkyl-1H-pyrrol-2(5H)-ones 5a–h

Primary amine (2.55 mmol, 2 equiv.) was added dropwise to a solution of ethyl 3-bromomethyl-4-oxopent-2-enoate 4 (0.3 g, 1.27 mmol) in bromobenzene (7 mL). The solution was heated for 0.5 to 2.5 h at 150°C. The solvent was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel.

Selected Data

4-Acetyl-1-benzyl-1H-pyrrol-2(5H)-one 5a. Yellow oil. Yield (0.14 g, 52%) (petroleum ether/ether, 6:4). IR (KBr), νmax (cm⁻¹): 2927, 1700, 1653, 1558, 668. ¹H NMR (300 MHz, CDCl₃): 7.40–7.30 (m, 6H, =C₆H, 5H₅Ar), 4.69 (s, 2H, CH₂Ph), 3.36 (d, 2H, 2JHH = 1.80 Hz, CH₂N), 2.18 (s, 3H, COCH₃); ¹³C NMR (75 MHz, CDCl₃): 190.8 (CO), 175.8 (CON), 142.6 (C₂q), 135.6 (C₅q), 129.1 (C₆q), 128.2 (C₅₆), 127.8 (C₅Ar), 119.7 (=CH), 46.1 (CH₂Ph), 35.6 (CH₂N), 25.0 (CH₃). HRMS calculated for [M+H]⁺ C₁₃H₁₄O₂N: 216.10191, found: 216.10180.

CONCLUSION

In summary, we have successfully developed a simple and efficient method for the synthesis of Z-ethyl 3-bromomethyl-4-oxopent-2-enoate 4, which was used directly in the production of 4-acetyl-1-alkyl-1H-pyrrol-2(5H)-ones 5a–h. The target compounds are important synthetic intermediates and may find some applications in the development of biologically active compounds.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. (a) Grison, C.; Genève, S.; Coutrot, P. Enantioselective synthesis of \( \alpha,\beta \)-unsaturated \( \gamma \)- and \( \delta \)-lactams. *Tetrahedron Lett.* 2001, 42, 3831–3834; (b) Groaning, M. D.; Meyers, A. I. Chiral nonracemic bicyclic lactams: Auxiliary-based asymmetric reactions. *Tetrahedron* 2000, 56, 9843–9873; (c) Dijkink, J.; Cintrat, J.-C.; Speckamp, W. N.; Hiemstra, H. Enantioselective synthesis of a key tricyclic intermediate en route to \((\pm)\)-gelisemine. *Tetrahedron Lett.* 1999, 40, 5919–5922; (d) Kuo, R.-Y.; Chang, F.-R.; Wu, Y.-C. A new propentdyopent derivative, rollipyrrole, from *Rollinia mucosa* Baill. *Tetrahedron Lett.* 2001, 42, 7907–7909; (e) Brower, J. O.; Lightner, D. A.; McDonagh, A. F. Aromatic congeners of bilirubin: Synthesis, stereochemistry, glucuronidation, and hepatic transport. *Tetrahedron* 2001, 57, 7813–7827; (f) Takabe, K.; Suzuki, M.; Nishi, T.; Hiyoshi, M.; Takamori, Y.; Yoda, H.; Mase, N. Convenient route to both enantiomers of chiral 5-hydroxy-\(1,5\)-dihydropyrrol-2-one: reverse enantioselectivity in lipase-catalyzed kinetic resolution. *Tetrahedron Lett.* 2000, 41, 9859–9863; (g) Kobayashi, J.; Sekiguchi, M.; Shimamoto, S.; Shigemori, H.; Ohsaki, A. Echinophyllins C-F: New nitrogen-containing clerodane diterpenoids from *Echinodorus macrophyllus*. *J. Nat. Prod.* 2000, 63, 1576–1579; (h) James, G. D.; Mills, S. D.; Pattenden, G. Total synthesis of pukeleimide A, a 5-ylidenepyrrol-2(5\(H\))-one from blue-green algae. *J. Chem. Soc., Perkin Trans. 1* 1993, 2581–2584.

2. Ma, D.; Ma, J.; Ding, W.; Dai, L. An improved procedure to homochiral cyclic statines. *Tetrahedron: Asymmetry* 1996, 7, 2365–2370.

3. (a) Casiraghi, G.; Spanu, P.; Rassu, G.; Pinna, L.; Ulgheri, F. Total syntheses of four isomers of \( cis \)-1,2-dihydroxypyrrolizidine. *J. Org. Chem.* 1994, 59, 2906–2909; (b) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. Synthesis and absolute configuration of the Aristotelia alkaloid peduncularine. *J. Am. Chem. Soc.* 1989, 111, 2588–2595.

4. (a) Iwasawa, N.; Maejama, K. A highly efficient synthesis of \((\pm)\)-PI-091 construction of the 4-alkoxy-2-butene-4-lactam skeleton from Fischer-type carbene complexes, alkynyllithiums, and tosyl isocyanate. *J. Org. Chem.* 1997, 62, 1918–1919; (b) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. Total synthesis of natural PI-091, a new platelet aggregation inhibitor of microbial origin. *J. Org. Chem.* 1996, 61, 2845–2852; (c) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Fujii, Y.; Kizu, H.; Boyd, M. R.; Boettner, F. E.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J.-C.; Michel, C. Isolation of dolastatins 10–15 from the marine mollusk *Dolabella auricularia*. *Tetrahedron* 1993, 49, 9151–9170; (d) Koehn, F. E.; Longley, R. E.; Reed, J. K. Microcolins A and B, new immunosuppressive peptides from the blue-green alga *Lyngbya majuscula*. *J. Nat. Prod.* 1992, 55, 613–619.

5. (a) Pelletier, S. W. (Ed.); *Alkaloids: Chemical and Biological Perspectives*; Wiley: New York, 1997; vol. 5; (b) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. Lythraceous alkaloids, X: Alkaloids of *Lagerstroemia subcostata* and *L.favriei*: A contribution to the chemotaxonomy. *Chem. Pharm. Bull.* 1978, 26, 2515–2521; (c) Wiedhopf, R. M.; Trumbull, E. R.; Cole, T. R. Antitumor agents from *Jatropha macrorhiza* (euphorbiaceae) I: Isolation and characterization of jatropham. *J. Pharm. Sci.* 1973, 62, 1206–1207.

6. Bosch, J.; Roca, T.; Catena, J.-L.; Lorens, O.; Perez, J.-J.; Lagunas, C.; Fernandez, A. G.; Miquel, I.; Fernandez-Serrat, A.; Farrerons, C. Synthesis and biological evaluation of 1,3,4-triaryl-3-pyrrolin-2-ones, a new class of selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett.* 2000, 10, 1745–1748.
7. (a) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Saltturo, F. G.; Tung, R. D.; Wright, L. L. Novel inhibitors of HIV protease: Design, synthesis, and biological evaluation of picomolar inhibitors containing cyclic P1/P2 scaffolds. *Bioorg. Med. Chem. Lett.* 2000, 10, 1159–1162; (b) Smith, A. B.; Hirschmann, R.; Pasternak, A.; Guzman, M. C.; Yokoyama, A.; Sprengeler, P. A.; Darke, P. L.; Emini, E. A.; Schleif, W. A. Pyrrolinone-based HIV protease inhibitors: Design, synthesis, and antiviral activity: Evidence for improved transport. *J. Am. Chem. Soc.* 1995, 117, 11113–11123.

8. (a) Li, S.-H.; Zhang, H.-J.; Qiu, S.-X.; Niu, X.-M.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H. S.; Farnsworth, N. R.; Sun, H. D. Vitexlactam A, a novel labdane diterpene lactam from the fruits of Vitex agnus-castus. *Tetrahedron Lett.* 2002, 43, 5131–5134; (b) Carpes, M. J. S.; Correia, C. R. D. Heck arylations of N-acyl-3-pyrroline and N-acyl-1,2,5,6-tetrahydropyridine with aryldiazonium salts. Short syntheses of aryl γ- and δ-lactams, baclofen, homobaclofen, and analogues. *Tetrahedron Lett.* 2002, 43, 741–744; (c) Bhattia, S. H.; Davies, G. M.; Hitchcock, P. B.; Loakes, D.; Young, D. W. Synthesis of reactive γ-lactams related to penicillins and cephalosporins. *J. Chem. Soc., Perkin Trans. 1* 1999, 2449–2454; (d) Davies, G. M.; Hitchcock, P. B.; Loakes, D.; Young, D. W. Synthesis of reactive γ-lactams related to penicillins and cephalosporins. *Tetrahedron Lett.* 1996, 37, 5601–5604; (e) Fishwick, C. W. G.; Foster, R. J.; Carr, R. E. A short dipolar cycloaddition approach to γ-lactam alkaloids from *Cynometra hankei*. *Tetrahedron Lett.* 1996, 37, 3915–3918; (f) Mattern, R.-H.; Gunasekera, S.; McConnell, O. Synthetic studies of microcolin B. *Tetrahedron* 1996, 52, 425–434; (g) Koehn, F. E.; McConnell, O. J.; Longley, R. E.; Sennett, S. H.; Reed, J. K. Analogs of the marine immunosuppressant microcolin A. Preparation and biological activity. *J. Med. Chem.* 1989, 32, 3181–3186; (h) Zhang, H.; Shigemori, H.; Ishibashi, M.; Kosaka, T.; Pettit, G. R.; Kamano, Y.; Kobayashi, J. A short dipolar cycloaddition approach to γ-lactam alkaloids from *Cynometra hankei*. *Tetrahedron* 1994, 50, 10201–10206; (i) Gamzu, E. R.; Hoover, T. M.; Gracon, S. I.; Ninteman, M. V. Recent development in 2-pyrrolidinone-containing nootropics. *Drug Dev. Res.* 1989, 18, 177–189; (j) Baldwin, J. E.; Freeman, R. T.; Lowe, C.; Schofield, C. J.; Lee, E. A γ-lactam analogue of the penems possessing antibacterial activity. *Tetrahedron* 1989, 45, 4537–4550; (k) Ikuta, H.; Shirotta, H.; Kobayashi, S.; Yamagishi, Y.; Yamada, K.; Yamatsu, I.; Katayama, K. Synthesis and antiinflammatory activities of 3-(3,5-di-tert-butyl-4-hydroxybenzylidene)pyrrolidin-2-ones. *J. Med. Chem.* 1987, 30, 1995–1998; (l) Baldwin, J. E.; Adlington, R. M.; Jones, R. H.; Schofield, C. J.; Zaracostas, C. γ-Lactam analogues of carbapenicillanic acids. *Tetrahedron* 1986, 42, 4879–4888; (m) Boyd, D. B.; Elzey, T. K.; Hatfield, L. D.; Kinnick, M. D.; Morin, J. M. Jr. γ-Lactam analogues of the penems. *Tetrahedron Lett.* 1986, 27, 3453–3456; (n) Belaud, C.; Roussakis, C.; Letourneux, Y.; El Alami, N.; Villiéras, J. Synthesis of potential cytotoxic α-methylene γ-lactams. *Synth. Commun.* 1985, 15, 1233–1243.

9. Pérard-Viret, J.; Souquet, F.; Manisse, M. L.; Royer, J. An expeditious total synthesis of (+)-jamtine using condensation between imine and acid anhydride. *Tetrahedron Lett.* 2010, 51, 96–98.

10. Reginato, G.; Capperucci, A.; Degl’Innocenti, A.; Mordini, A.; Pecchi, S. Stannylcupration of γ-heterosubstituted acetylenic esters: A new route to 4-stannylated five membered N- and O-heterocycles. *Tetrahedron* 1995, 51, 2129–2136.

11. Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. Pyrrolidine and α-methylene-α-lactam from the cyclization of α-(alkylaminoethyl)acrylate: Synthesis of aza-sarkomycins. *Tetrahedron Lett.* 1987, 28, 6675–6678.

12. Besbes, R.; Villiéras, M.; Amri, H. Improved synthesis and reaction of dimethyl α-(bromomethyl) fumarate with primary amines. *Indian J. Chem., Sect. B* 1997, 36B, 5–8.
13. Torii, S.; Inokuchi, T.; Kubota, M. A practical access to methyl 3,3-dimethoxypropionates and \(N\)-protected \(\beta\)-aminoacrylates and \(\beta\)-aminoacrylonitrile by using electrochemical procedure. *J. Org. Chem.* **1985**, *50*, 4157–4160.

14. Galeazzi, R.; Martelli, G.; Natali, D.; Orena, M.; Rinaldi, S. Chiral 3-hydroxypyrrolidin-2-ones, Part 2: Stereo-divergent synthesis of conformationally restricted analogues of \(\beta\)-homoserine. *Tetrahedron: Asymmetry* **2005**, *16*, 1779–1787.

15. Deredas, D.; Albrecht, L.; Krawczyk, H. An efficient synthesis of \(\beta,\gamma,\gamma\)-trisubstituted-\(\alpha\)-diethoxyphosphoryl-\(\gamma\)-lactams: A convenient approach to \(\alpha\)-methylene-\(\gamma\)-lactams. *Tetrahedron Lett.* **2013**, *54*, 3088–3090.

16. Gein, V. L.; Kasimova, N. N. Three-component condensation of methyl acylpyruvates with aromatic aldehydes and ethylenediamine: Chemical properties of the products. *Russ. J. Gen. Chem.* **2005**, *75*, 254–260.

17. Liu, R.; Winston-McPherson, G. N.; Yang, Z.-Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. Generation of rhodium(I) carbenes from ynamides and their reactions with alkenes and alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 8201–8204.

18. (a) Villiéras, J.; Rambaud, M. Wittig–Horner reaction in heterogeneous media, 1: An easy synthesis of ethyl \(\alpha\)-hydroxymethylacrylate and ethyl \(\alpha\)-halomethylacrylates using formaldehyde in water. *Synthesis* **1982**, 924–926; (b) Villiéras, J.; Rambaud, M.; Graff, M. Wittig–Horner reaction in heterogeneous media, VII: A new strategy for the total syntheses of the royal jelly acid and the queen substance of honey bee. *Synth. Commun.* **1985**, *15*, 569–580; (c) Ben Ayed, T.; Amri, H. A convenient synthesis of \(\alpha\)-functional alkyl vinyl ketones. *Synth. Commun.* **1995**, *25*, 3813–3819.

19. Loeffler, A.; Pratt, R. D.; Pucknat, J.; Gelbart, G.; Dreiding, A. S. Préparation des \(\alpha\)-Méthyle Butyrolactones par Réaction de Reformatsky: Synthèse de l’Acide Protolichesterique. *Chimia* **1969**, *23*, 413–416.

20. Welch, S. C.; Gruber, J. M. Synthesis of C-13-substituted retinoic acid analogs. *J. Org. Chem.* **1982**, *47*, 385–389.

21. Nelson, R. P.; McEuen, J. M.; Lawton, R. G. \(\alpha,\alpha\prime\)-annulation of cyclic ketones: Synthesis of bicyclo[3.2.1]octane derivatives. *J. Org. Chem.* **1969**, *34*, 1225–1229.

22. Dekkers, A. W. J. D.; Speckman, W. N.; Huisman, H. O. Addition of diethyl 2-bromo-mesaconate to \(N\)-tosylpiperidone enamine. *Tetrahedron Lett.* **1971**, *12*, 489–492.

23. Labuschange, A. J. H.; Malherbe, J. S.; Meyer, C. J.; Schneider, D. F. General synthesis of symmetrical and unsymmetrical organic sulphides under non-basic reaction conditions. *J. Chem. Soc., Perkin Trans. 1* **1973**, *1978*, 955–961, and references cited therein.

24. Garbers, C. F.; Labuschagne, A. J. H.; Meyer, C. J.; Schneider, D. F. Stereospecific formation of a vinyl sulphide via a sulphonium ylide–salt coupling reaction. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2016–2019.

25. Sasaki, T.; Kanematsu, K.; Kakehi, A.; Ito, G.-I. Molecular design by cycloaddition reactions, part IX: Further investigation of the cycloaddition reactions of pyridinium allylides [1-(1-pyridino)prop-2-enides] to give indolizines. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2089–2091.

26. Zhujin, L.; Guobin, R. Reaction of \(\beta\)-methyl-\(\gamma\)-oxo-\(\alpha\),\(\beta\)-unsaturated esters with NBS. *Chin. J. Org. Chem.* **1986**, *6*, 363–365.

27. Ben Ayed, T.; Amri, H.; El Gaied, M. M. Addition of bromine to \(\beta\prime\)-(functional alkyl) \(\alpha\),\(\beta\)-unsaturated esters stereoselective synthesis of \(\beta\)-haloderivatives. *Tetrahedron* **1991**, *47*, 9621–9628.

28. Ben Gharbia, S.; Besbes, R.; Villiéras, M.; Amri, H. Selected reaction of (Z)-dimethyl \(\alpha\)-(bromomethyl)fumarate with secondary amines. *Synth. Commun.* **1996**, *26*, 1685–1692.