Allenyl Ketones as Versatile Michael Acceptors for the Addition of Chelated Enolates

Simon Lucas, Uli Kazmaier*

Institut für Organische Chemie, Universität des Saarlandes, 66123 Saarbrücken, Germany
Fax +49(681)3022409; E-mail: u.kazmaier@mx.uni-saarland.de

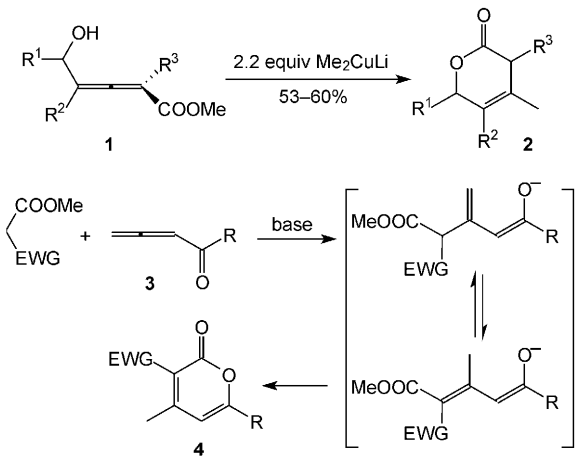
Received 17 November 2005

Abstract: Chelated amino acid ester enolates undergo clean 1,4-addition towards allenyl ketones **9**, giving rise to unsaturated δ-keto amino acid esters **12** at low temperature. If the reaction is allowed to warm to room temperature, the enolate intermediates **A** undergo cyclization towards the corresponding α-pyrones **13**.

Key words: amino acids, chelates, enolates, Michael addition, MIRC

Michael additions belong to the most popular C–C-coupling reactions, especially because of the wide range of nucleophiles and Michael acceptors which can be coupled by this protocol.[1] Besides α,β-unsaturated esters and ketones, also allenes bearing electron-withdrawing groups such as allenyl ketones,[2] sulfones[3] or nitriles[4] can be used.[5] In principle, the 1,4-addition towards α,β-unsaturated ketones has to compete with the 1,2-aldol addition. Both processes are reversible, and therefore it is sometimes advantageous to remove some of the intermediates by subsequent reactions, such as cyclizations from the equilibrium. These so-called 'Michael addition induced ring-closing' (MIRC) reactions became very popular over the last years.[6] Herein, also allenyl ketones can be used and several applications towards the synthesis of heterocycles are reported so far. For example, Knight et al. reported on a 1,4-addition of Me_2CuLi towards allene **1**, followed by a subsequent lactonization giving rise to lactone **2** (Scheme 1).[7] Ma et al. were able to show, that acceptor-substituted ester enolates undergo Michael addition towards allenyl ketones **3**. Subsequent isomerization–cyclization of the intermediary enolates provides α-pyrones **4** in good to excellent yields, depending on the reaction parameters and the coupling partners used.[8]

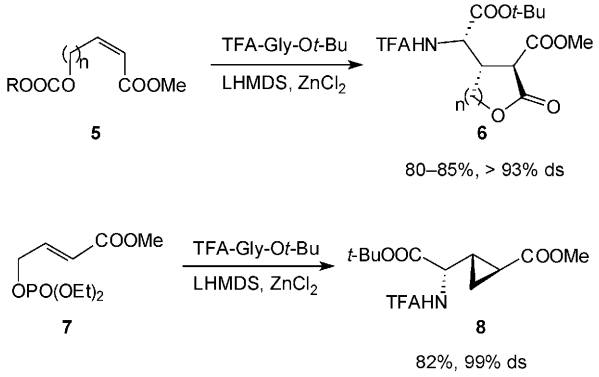
Our group is involved in amino acid synthesis, investigating reactions of chelated amino acid ester enolates.[9] These stabilized enolates are also versatile nucleophiles for 1,4-additions[10] or MIRC reactions.[11] For example, Michael addition of trifluoroacetylated (TFA-) glycinate towards α,β-unsaturated esters **5** bearing a carbonate functionality gives rise to cyclic glutamate derivative **6**, while with the corresponding phosphonate **7** the cyclopropyl amino acid ester **8** was formed (Scheme 2). Therefore, we were interested to see, if our chelated enolates would react also with



Scheme 1 Michael addition induced ring-closure of allenic ketones.

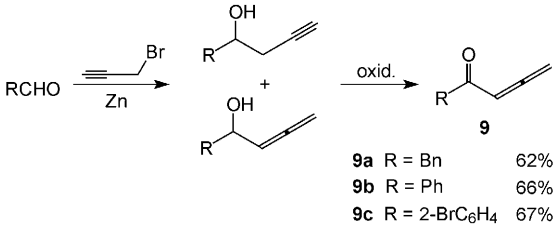
allenyl ketones, and if the enolate intermediates formed might undergo cyclization according to Ma et al. (Scheme 1).

For this purpose we synthesized several allenyl ketones **9** (Scheme 3).[12] The ketones **9a** and **9b** were obtained from the corresponding aldehyde and propargyl bromide in a Barbier-type reaction,[13] followed by a Dess–Martin periodinane oxidation. During the chromatographical purification the primary formed propargylic ketone isomerized to the required allenyl ketone.[14] Ketone **9c** was obtained from the corresponding allenylalcohol[15] via oxidation with SIBX.[16]



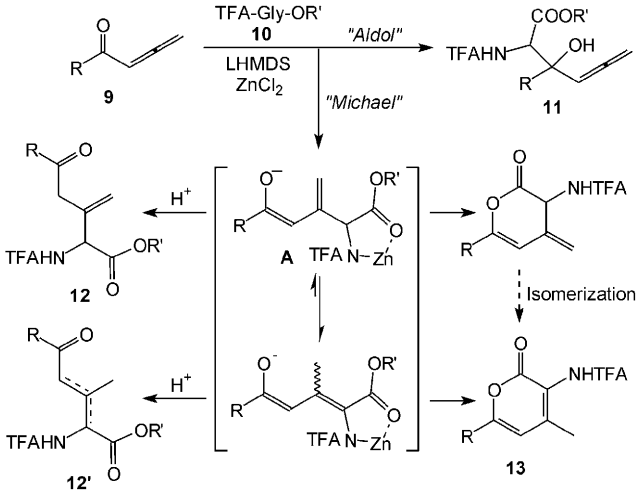
Scheme 2 Michael addition induced ring-closure of chelated enolates.

SYNLETT 2006, No. 2, pp 0255–0258
Advanced online publication: 23.12.2005
DOI: 10.1055/s-2005-923591; Art ID: G36605ST



Scheme 3 Synthesis of allenylketones **9**.

In principle, several possibilities have to be considered. The enolate obtained from **10** can either undergo an aldol reaction with ketone **9** giving rise to allenyl β-hydroxy amino acid ester **11**, or it can undergo the desired 1,4-addition, forming intermediate **A** (Scheme 4). Protonation should provide δ-keto amino acid derivative **12** or a derivative with an isomerized double bond (**12′**). On the other hand, if cyclization occurs, one might expect **13** as a major product, also with an isomerized double bond. Isomerization of the external double bond to a thermodynamically more stable one has to be considered under these basic conditions on any stage.



Scheme 4 Possible reaction pathways.

For our first investigations we chose the *tert*-butyl ester (R′ = *t*-Bu) of **10** (**10a**), because this nucleophile gave the best results in several other reactions, including the MIRC.[11] We hoped that with the sterically demanding ester the cyclization step can be suppressed and to obtain the linear amino acid derivative **12**. And indeed, if the reaction with ketone **9a** was kept at –78 °C and quenched at this temperature, the linear product **12aa** was obtained preferentially, together with aldol product **11aa**[17] as the minor compound (Table 1, entry 1). Unfortunately, the Michael addition at this temperature was rather sluggish and no complete consumption of the allenyl ketone could be observed. Therefore, the yield was only moderate (48%). It could be slightly increased by increasing the amount of nucleophile used (entry 2), but still there was some starting material left (16%). This slow Michael addition might explain why the aldol product from the rather unreactive ketone was obtained. Warming the reaction mixture to room temperature did not increase the yield either, but resulted in the formation of the lactone **13a** as sole product (entry 3). No aldol product could be observed under these conditions.[18]

This suggests that the aldol reaction is reversible, what might be also the case for the Michael addition. To increase the reaction rate and the tendency for cyclization we decided to switch to the sterically less hindered methyl ester **10b** (entries 4–10). And indeed, no aldol reaction was observed anymore, and the yield was significantly increased, especially with a slight excess of nucleophile (entries 4 and 5). The reaction was complete after three hours at –78 °C, and the linear Michael adduct **12ab** could be obtained in high yield by quenching the reaction at this temperature (entry 6). On the other hand, warming the reaction mixture to room temperature resulted in a clean cyclization–isomerization giving rise to α-pyrone **13a**. Prolonging the reaction time at low temperature does not increase the yield but favors decomposition reactions. Changing the chelated metal salt does also give no improvement. For example, with $TiCl(O\textit{i}\text{-}Pr)_3$ the yield dropped to 26%. Therefore, we applied these optimized conditions also for the other allenic substrates **9b** and **9c** (entries 7–10). And again, the Michael adducts **12** were obtained exclusively at –78 °C, and the α-pyrones **13** by warming to room temperature.[19] The yields were reproducible in the range of 54–84% for the Michael adducts and 61–70% for the α-pyrones.

In conclusion, we have shown that chelated enolates of amino acid esters can be used as nucleophiles in Michael additions towards allenylketones, and that the Michael adducts undergo clean cyclization–isomerization to α-pyrones by warming the reaction mixture to room temperature. Applications of this protocol for the synthesis of even more complex amino acids and derivatives are currently under investigation.

Acknowledgment

Financial support by the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

(1) (a) Yamamoto, Y. *Stereoselective Synthesis*, In *Houben–Weyl: Methoden der organischen Chemie*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, New York, **1996**, 2041–2067. (b) Feringa, B. L.; Jansen, J. F. G. A. *Stereoselective Synthesis*, In *Houben–Weyl: Methoden der organischen Chemie*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, New York, **1996**, 2104–2156.

(2) (a) Chinkov, N.; Morlender-Vais, N.; Marek, I. *Tetrahedron Lett.* **2002**, *43*, 6009. (b) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677.

Table 1 Addition of Chelated Enolates towards Allenylketones **9**

Entry	Ketone		TFA-Gly-OR′			Reaction conditions	Yield					
	9	R	**10**	R′	Equiv		**11**	(%)	**12**	(%)	**13**	(%)
1	**9a**	Bn	**10a**	*t*-Bu	0.95	THF, –78 °C, 24 h	**11aa**	13	**12aa**	48		–
2	**9a**	Bn	**10a**	*t*-Bu	1.25	THF, –78 °C, 24 h	**11aa**	14	**12aa**	54		–
3	**9a**	Bn	**10a**	*t*–Bu	0.95	THF, –78 °C to r.t., 12 h					**13a**	44
4	**9a**	Bn	**10b**	Me	0.95	THF, –78 °C to r.t., 12 h					**13a**	63
5	**9a**	Bn	**10b**	Me	1.25	THF, –78 °C to r.t., 12 h					**13a**	70
6	**9a**	Bn	**10b**	Me	1.25	THF, –78 °C, 3 h			**12ab**	84		
7	**9b**	Ph	**10b**	Me	1.25	THF, –78 °C, 3 h			**12bb**	69		
8	**9b**	Ph	**10b**	Me	1.25	THF, –78 °C to r.t., 12 h					**13b**	66
9	**9c**	2–BrC_6H_4	**10b**	Me	1.25	THF, –78 °C, 3 h			**12cb**	70		
10	**9c**	2–BrC_6H_4	**10b**	Me	1.25	THF, –78 °C to r.t., 12 h					**13c**	61

(3) (a) Padwa, A.; Yeske, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 1617. (b) Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K. *J. Org. Chem.* **1986**, *51*, 5100. (c) Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R. *J. Org. Chem.* **1990**, *55*, 4595. (d) Padwa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386.

(4) Yoneda, R.; Inagaki, N.; Harusawa, S.; Kurihara, T.; Takushi, T. *Chem. Pharm. Bull.* **1992**, *40*, 21.

(5) (a) *Allenes in Organic Synthesis*; Schuster, H. F.; Copolla, G. M., Eds.; Wiley: New York, **1984**. (b) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, **2004**.

(6) (a) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609. (b) Prempree, P.; Radviroongit, S.; Thebtaranonth, Y. *J. Org. Chem.* **1983**, *48*, 3553.

(7) Knight, J. G.; Ainge, S. W.; Eastman, T. P.; Harwood, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3188.

(8) (a) Ma, S.; Yin, S.; Tao, F. *Org. Lett.* **2002**, *4*, 505. (b) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996.

(9) Reviews: (a) Kazmaier, U. *Amino Acids* **1996**, *11*, 283. (b) Kazmaier, U. *Liebigs Ann./Recl.* **1997**, 285. (c) Kazmaier, U. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 351.

(10) (a) Mendler, B.; Kazmaier, U. *Org. Lett.* **2005**, *7*, 1715. (b) Mendler, B.; Kazmaier, U. *Synthesis* **2005**, 2239.

(11) (a) Pohlman, M.; Kazmaier, U. *Org. Lett.* **2003**, *5*, 2631. (b) Mendler, B.; Kazmaier, U.; Huch, V.; Veith, M. *Org. Lett.* **2005**, *7*, 2643.

(12) NMR Spectroscopic Data of Allenylketones **9**.
Compound **9a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 2 H, 5-H), 5.27 (d, $^4J_{1,3}$ = 6.6 Hz, 2 H, 1-H), 5.81 (t, $^4J_{3,1}$ = 6.6 Hz, 1 H, 3-H), 7.21–7.32 (m, 5 H, 7-H, 8-H, 9-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.9 (t, C-5), 79.8 (t, C-1), 95.4 (d, C-3), 126.8 (d, C-9), 128.4 (d, C-7), 129.4 (d, C-8), 134.5 (s, C-6), 197.5 (s, C-4), 217.1 (s, C-2).
Compound **9b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.24 (d, $^4J_{1,3}$ = 6.6 Hz, 2 H, 1-H), 6.43 (t, $^4J_{3,1}$ = 6.6 Hz, 1 H, 3-H), 7.44 (m, 2 H, 7-H), 7.54 (m, 1 H, 8-H), 7.88 (dd, $^3J_{6,7}$ = 8.2 Hz, $^4J_{6,8}$ = 1.3 Hz, 2 H, 6-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 79.2 (t, C-1), 93.2 (d, C-3), 128.6 (d, C-6), 128.7 (d, C-7), 132.8 (d, C-8), 137.5 (s, C-5), 191.0 (s, C-4), 217.1 (s, C-2).
Compound **9c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.07 (d, $^4J_{1,3}$ = 6.6 Hz, 2 H, 1-H), 6.13 (t, $^4J_{3,1}$ = 6.6 Hz, 1 H, 3-H), 7.23 (m, 1 H, 8-H), 7.51 (m, 1 H, 7-H), 7.45 (m, 1 H, 9-H), 7.54 (m, 1 H, 6-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 79.9 (t, C-1), 96.8 (d, C-3), 119.0 (s, C-10), 126.9 (d, C-8), 128.7 (d, C-6), 131.1 (d, C-7), 133.1 (d, C-9), 140.5 (s, C-5), 194.4 (s, C-4), 218.8 (s, C-2).

(13) Wu, W.-L.; Yao, Z.-J.; Li, Y.-L.; Li, J.-C.; Xia, Y.; Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 3257.

(14) (a) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295. (b) Hashmi, A. S. K.; Schwarz, L.; Bolte, M. *Eur. J. Org. Chem.* **2004**, 1923.

(15) Kazmaier, U.; Lucas, S.; Klein, M. *Adv. Synth. Catal.* **2005**, submitted.

(16) Ozanne, A.; Pouységu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903.

(17) NMR Spectroscopic Data of Aldol Product **11aa**.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (s, 9 H, 15-H), 2.74 (s, 1 H, OH), 2.96 (d, $^2J_{8,8'}$ = 13.6 Hz, 1 H, 8-H), 3.12 (d, $^2J_{8',8}$ = 13.6 Hz, 1 H, 8′-H), 4.58 (d, $^3J_{3,NH}$ = 9.2 Hz, 1 H, 3-H), 4.75 (dd, $^2J_{7,7'}$ = 11.4 Hz, $^4J_{7,5}$ = 6.6 Hz, 1 H, 7-H), 4.89 (dd, $^2J_{7',7}$ = 11.4 Hz, $^4J_{7',5}$ = 6.9 Hz, 1 H, 7′-H), 5.17 (dd, $^4J_{5,7}$ = 6.6 Hz, $^4J_{5,7'}$ = 6.9 Hz, 1 H, 5-H), 7.00 (d, $^3J_{NH,3}$ = 9.2 Hz, 1 H, NH), 7.17–7.32 (m, 5 H, 10-H, 11-H, 12-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.0 (q, C-15), 44.4 (t, C-8), 58.8 (d, C-3), 75.2 (t, C-7), 80.2 (s, C-14), 84.3 (s, C-4), 94.8 (d, C-5), 127.1 (d, C-12), 128.2 (d, C-11), 130.9 (d, C-10), 135.0 (s, C-9), 167.7 (s, C-13), 206.3 (s, C-6). Signals of the TFA protecting group are not detectable.

(18) **General Procedure for Michael Additions of Chelated Enolates.**
Hexamethyldisilazane (280 mg, 1.73 mmol) was diluted in a Schlenk tube under argon with THF (1.5 mL). The solution was cooled to –20 °C before a solution of *n*-BuLi (1 mL, 1.6 M, 1.6 mmol) was added slowly. Stirring was continued for further 20 min, before the cooling bath was removed and the mixture allowed to warm to r.t. In another Schlenk flask a solution of the protected amino acid ester (0.63 mmol) in THF (3 mL) was cooled to –78 °C, before the fresh prepared LHMDS solution was added slowly via syringe. After stirring for 15 min at –78 °C a solution of $ZnCl_2$ (94 mg, 0.69 mmol) in THF (1 mL) was added and stirring was continued for further 45 min, before a solution of the allenyl ketone **9** (0.5 mmol) in THF (1 mL) was added. The progress of the reaction was monitored by TLC, and after complete

consumption of the ketone (2–3 h) the reaction mixture was diluted with Et_2O and hydrolyzed with 1 N $KHSO_4$ giving rise to the expected ketone **12**.[18] The aqueous layer was extracted twice with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography or crystallization. To obtain the α-pyrones **13**[19] the reaction mixture was allowed to warm to r.t. before work-up.

Analytical Data of Michael Addition Products 12.

Compound **12aa**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, 15-H), 3.28 (d, $^2J_{5,5'}$ = 17.0 Hz, 1 H, 5-H), 3.34 (d, $^2J_{5',5}$ = 17.0 Hz, 1 H, 5′-H), 3.75 (s, 2 H, 7-H), 4.85 (d, $^3J_{3,NH}$ = 6.6 Hz, 1 H, 3-H), 5.10 (s, 1 H, 12-H$_{trans}$), 5.34 (s, 1 H, 12-H$_{cis}$), 7.19 (dd, $^3J_{9,10}$ = 8.2 Hz, $^4J_{9,11}$ = 1.3 Hz, 2 H, 9-H), 7.27 (tt, $^3J_{11,10}$ = 7.3 Hz, $^4J_{11,9}$ = 1.3 Hz, 1 H, 11-H), 7.33 (m, 2 H, 10-H), 7.87 (d, $^3J_{NH,3}$ = 6.6 Hz, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7 (q, C-15), 49.1 (t, C-5), 49.8 (t, C-7), 58.1 (d, C-3), 83.6 (s, C-14), 115.7 (q, $^1J_{1,F}$ = 287.9 Hz, C-1), 121.6 (t, C-12), 127.3 (d, C-11), 128.9 (d, C-10), 129.4 (d, C-9), 133.4 (s, C-4), 135.6 (s, C-8), 156.6 (q, $^2J_{2,F}$ = 38.4 Hz, C-2), 167.5 (s, C-13), 206.5 (s, C-6). HRMS (CI): *m/z* calcd for $C_{19}H_{23}F_3NO_4$ [M + H]$^+$: 386.1498; found: 386.1539.

Compound **12ab**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.28 (d, $^2J_{5,5'}$ = 17.3 Hz, 1 H, 5-H), 3.37 (d, $^2J_{5',5}$ = 17.3 Hz, 1 H, 5′-H), 3.70 (s, 3 H, 14-H), 3.72 (s, 2 H, 7-H), 5.00 (d, $^3J_{3,NH}$ = 6.6 Hz, 1 H, 3-H), 5.11 (s, 1 H, 12-H$_{trans}$), 5.36 (s, 1 H, 12-H$_{cis}$), 7.19 (dd, $^3J_{9,10}$ = 8.2 Hz, $^4J_{9,11}$ = 1.3 Hz, 2 H, 9-H), 7.28 (tt, $^3J_{11,10}$ = 7.3 Hz, $^4J_{11,9}$ = 1.3 Hz, 1 H, 11-H), 7.34 (m, 2 H, 10-H), 8.01 (d, $^3J_{NH,3}$ = 6.6 Hz, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.0 (t, C-5), 49.8 (t, C-7), 53.0 (q, C-14), 57.5 (d, C-3), 115.6 (q, $^1J_{1,F}$ = 287.9 Hz, C-1), 122.4 (t, C-12), 127.4 (d, C-11), 128.9 (d, C-10), 129.4 (d, C-9), 133.2 (s, C-4), 134.9 (s, C-8), 156.7 (q, $^2J_{2,F}$ = 37.4 Hz, C-2), 169.0 (s, C-13), 206.8 (s, C-6). HRMS (CI): *m/z* calcd for $C_{16}H_{17}F_3NO_4$ [M + H]$^+$: 343.1130; found: 344.1120.

Compound **12bb**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, 13-H), 3.82 (d, $^2J_{5,5'}$ = 17.4 Hz, 1 H, 5-H), 3.94 (d, $^2J_{5',5}$ = 17.4 Hz, 1 H, 5′-H), 5.12 (d, $^3J_{3,NH}$ = 6.4 Hz, 1 H, 3-H), 5.29 (s, 1 H, 11-H$_{trans}$), 5.48 (s, 1 H, 11-H$_{cis}$), 7.48 (m, 2 H, 9-H), 7.60 (tt, $^3J_{10,9}$ = 7.6 Hz, $^4J_{10,8}$ = 1.2 Hz, 1 H, 10-H), 7.95 (dd, $^3J_{8,9}$ = 8.5 Hz, $^4J_{8,10}$ = 1.2 Hz, 2 H, 8-H), 8.19 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.1 (t, C-5), 53.1 (q, C-13), 57.9 (d, C-3), 115.6 (q, $^1J_{1,F}$ = 286.9 Hz, C-1), 122.9 (t, C-11), 128.4 (d, C-8), 128.8 (d, C-9), 133.9 (d, C-10), 135.4 (s, C-4), 135.9 (s, C-7), 156.8 (q, $^2J_{2,F}$ = 37.6 Hz, C-2), 169.1 (s, C-12), 198.4 (s, C-6). HRMS (CI): *m/z* calcd for $C_{15}H_{14}F_3NO_4$ [M]$^+$: 329.0837; found: 329.0856.

Compound **12cb**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, 15-H), 3.78 (d, $^2J_{5,5'}$ = 17.8 Hz, 1 H, 5-H), 3.86 (d, $^2J_{5',5}$ = 17.8 Hz, 1 H, 5′-H), 5.12 (d, $^3J_{3,NH}$ = 6.7 Hz, 1 H, 3-H), 5.32 (s, 1 H, 13-H$_{trans}$), 5.46 (s, 1 H, 13-H$_{cis}$), 7.29–7.40 (m, 3 H, 9-H, 10-H, 11-H), 7.59 (d, $^3J_{8,9}$ = 7.9 Hz, 1 H, 8-H), 7.93 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.7 (t, C-5), 53.2 (q, C-15), 57.6 (d, C-3), 115.5 (q, $^1J_{1,F}$ = 287.9 Hz, C-1), 118.6 (s, C-12), 122.9 (t, C-13), 127.5 (d, C-8), 128.7 (d, C-9), 132.2 (d, C-10), 133.8 (d, C-11), 134.6 (s, C-4), 140.5 (s, C-7), 156.7 (q, $^2J_{2,F}$ = 37.6 Hz, C-2), 169.0 (s, C-14), 201.9 (s, C-6). HRMS (CI): *m/z* calcd for $C_{15}H_{14}{}^{79}BrF_3NO_4$ [M + H]$^+$: 408.0074; found: 408.0066.

(19) **Analytical Data of α-Pyrones 13.**

Compound **13a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, 13-H), 3.78 (s, 2 H, 8-H), 5.84 (s, 1 H, 6-H), 7.23 (dd, $^3J_{10,11}$ = 6.9 Hz, $^4J_{10,12}$ = 1.6 Hz, 2 H, 10-H), 7.29 (tt, $^3J_{12,11}$ = 7.3 Hz, $^4J_{12,10}$ = 1.6 Hz, 1 H, 12-H), 7.34 (dd, $^3J_{11,12}$ = 7.3 Hz, $^4J_{11,10}$ = 6.9 Hz, 2 H, 11-H), 8.38 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2 (q, C-13), 39.6 (t, C-8), 107.5 (d, C-6), 115.6 (q, $^1J_{C,F}$ = 287.9 Hz, C-1), 115.9 (s, C-5), 127.6 (d, C-10), 128.9 (d, C-12), 129.2 (d, C-11), 134.5 (s, C-9), 150.1 (s, C-4), 155.5 (q, $^2J_{C,F}$ = 37.4 Hz, C-2), 160.4 (s, C-7), 161.6 (s, C-3). Anal. Calcd for $C_{15}H_{12}F_3NO_3$ (311.26): C, 57.88; H, 4.50; N, 3.89. Found: C, 57.53; H, 4.44; N, 3.93. HRMS (CI): *m/z* calcd for $C_{15}H_{13}F_3NO_3$ [M + H]$^+$: 312.0774; found: 312.0811.

Compound **13b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.14 (s, 3 H, 12-H), 7.16 (s, 1 H, 6-H), 7.53 (m, 3 H, 10-H, 11-H), 7.87 (m, 2 H, 9-H), 11.01 (br s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.8 (q, C-12), 104.9 (d, C-6), 115.8 (q, $^1J_{1,F}$ = 287.9 Hz, C-1), 116.8 (s, C-5), 125.5 (d, C-10), 129.2 (d, C-11), 130.4 (d, C-9), 131.0 (s, C-8), 152.3 (s, C-4), 155.3 (q, $^2J_{2,F}$ = 36.5 Hz, C-2), 156.9 (s, C-7), 158.1 (s, C-3). HRMS (CI): *m/z* calcd for $C_{14}H_{10}F_3NO_3$ [M]$^+$: 297.0595; found: 297.0604.

Compound **13c**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.14 (s, 3 H, 14-H), 6.76 (s, 1 H, 6-H), 7.47 (m, 1 H, 10-H), 7.54 (m, 1 H, 11-H), 7.65 (dd, $^3J_{12,11}$ = 7.6 Hz, $^4J_{12,10}$ = 1.9 Hz, 1 H, 12-H), 7.80 (dd, $^3J_{9,10}$ = 7.9 Hz, $^4J_{9,11}$ = 1.0 Hz, 1 H, 9-H), 11.04 (br s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.7 (q, C-14), 109.7 (d, C-6), 115.8 (q, $^1J_{1,F}$ = 287.9 Hz, C-1), 117.5 (s, C-5), 121.0 (s, C-13), 128.2 (d, C-10), 131.4 (d, C-9), 132.4 (d, C-12), 132.6 (d, C-11), 133.6 (s, C-8), 151.8 (s, C-4), 157.0 (s, C-7), 158.1 (s, C-3). C-2 was not detectable. HRMS (CI): *m/z* calcd for $C_{15}H_9{}^{79}BrF_3NO_3$ [M]$^+$: 374.9718; found: 374.9709.