Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 611–614

TETRAHEDRON LETTERS

Stereoselective synthesis of 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones, a new class of non-biaryl atropisomeric compounds. Part 1

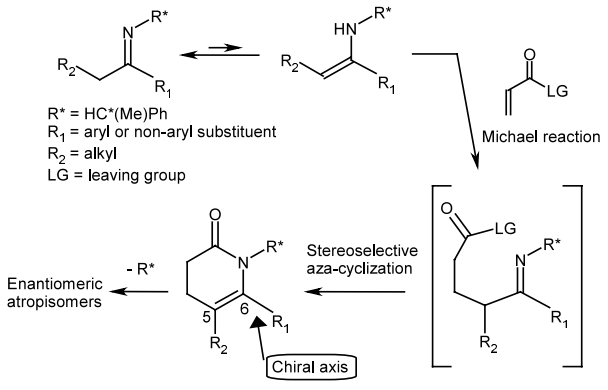
Ivan Jabin,* Nicolas Monnier-Benoit, Stéphane Le Gac and Pierre Netchitaïlo

URCOM, Université du Havre, Faculté des Sciences et Techniques, 25 rue Philippe Lebon, BP 540, 76058 Le Havre Cedex, France

Received 12 July 2002; revised 6 September 2002; accepted 9 September 2002

Abstract—Atropisomeric 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones have been synthesized stereoselectively from chiral imines through a Michael reaction and a subsequent stereoselective azacyclization. A thermal study has shown that epimerization of the chiral axis can not take place even at high temperature. © 2002 Elsevier Science Ltd. All rights reserved.

Atropisomerism is a phenomenon which results from slow rotation about a single bond.[1] Enantiomerically pure atropisomers of axially chiral biaryls have been widely used as ligands for asymmetric metal-catalyzed reactions.[2] However, their synthesis remains a challenge and thus non-biaryls atropisomers, i.e. chiral anilides, 1-naphtamides and benzamides, have attracted much attention in recent literature.[3] Applications as chiral ligands or auxiliaries of these axially chiral amides have been reported but their usefulness is still limited by the lack of general methods that can provide them as enantiomerically pure atropisomers. Indeed, enantioselective syntheses of these chiral amides are rare[4] and they are generally obtained by resolution.[5] Consequently, the discover of new classes of easily accessible atropisomeric compounds which can offer opportunities for a wide variety of structural changes and especially for the introduction of chelating groups is of great interest in asymmetric synthesis.



Scheme 1.

We recently reported an efficient and expedient method for the stereoselective synthesis of cyclic enamides through a tandem process consisting in a Michael reaction of chiral imines, reacting through their tautomeric enamine form, followed by an aza-cyclization step.[6] We have set out to produce 5,6-disubstituted-3,4-dihydro-1*H*-pyridin-2-ones by this route and to study their ability to generate atropisomerism by restricting rotation of the exocyclic single bond bearing the 6-substitutent (Scheme 1). Indeed, the enamide system being almost planar, atropisomerism could arise with suitable bulky substituents on the 6-position by steric or electronic interactions with the R_2 substituent and/or the substituent borne by the nitrogen. Our aim was to have the possibility of an easy introduction of chelating groups on the 6-substituent so we envisaged either 6-aryl or 6-non-aryl substituents. A chiral auxiliary has been anchored on the starting imine, hoping it will lead to a stereoselective production of atropisomers under kinetic control during the aza-cyclization step or under thermodynamic control by thermal equilibration of the products. The presence of the chiral auxiliary in the product should also permit an easy separation of the atropisomers which are diastereomers and could prevent rotation of the chiral axis by thermodynamic resistance. An easy removal of R* was required for a

* Corresponding author. Tel.: +332 32 74 43 94; fax: +332 32 74 43 91; e-mail: ivan.jabin@univ-lehavre.fr

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02583-2

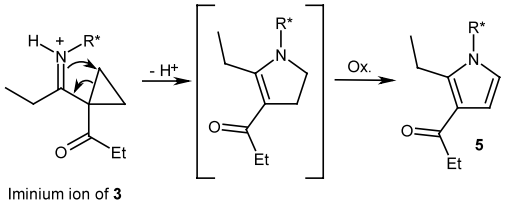
straightforward access to enantiomeric atropisomers. Thus, optically active 1-phenylethylamine has been chosen as the chiral auxiliary since we already performed the cleavage of its chiral moiety [i.e. HC*(Me)Ph] on closely related structures[6a,c,f] (Scheme 1).

We communicate here our preliminary work concerning the stereoselective synthesis of the 6-non-aryl-substituted-3,4-dihydro-1*H*-pyridin-2-ones, a new class of atropisomeric compounds, and the study of their atropisomerism.

We decided to test the feasibility of our approach with the diketone **1** and the keto-ester **2**, both incorporating a cyclopropyl moiety.[7] Indeed, a quaternary carbon atom on the α-position of the future imine position was required in order to prevent formation of the non desired regioisomeric enamine tautomeric form (a more stable conjugated enaminone in this case). The starting chiral imines **3** and **4** were prepared classically[8] from compounds **1** and **2** respectively and optically active (*S*)-1-phenylethylamine (Scheme 2).

Imines **3** and **4** revealed to be unstable under acidic conditions, either during the course of the reaction (presence of TFA), in $CHCl_3$ or on silica gel. Indeed, in both cases GC-MS, ^{1}H NMR and TLC analyses of the crude reaction mixtures have shown the formation of traces of their respective degradation product. Moreover, an attempt of purification of imine **3** by flash chromatography (FC) on silica gel led, besides the expected imine **3**[9] (42% yield), to the same by-product in higher amount. This unexpected degradation compound has been isolated and its ^{1}H NMR and MS spectra were consistent with the pyrrolic structure **5**.[10] The origin of this latter can be tentatively rationalized by a cyclopropyl rearrangement initiated by the formation of the iminium ion of **3**. The resulting dihydropyrrole should aromatize upon air oxidization giving the more stable pyrrole **5** (Scheme 3). A careful literature survey has shown that such an acid-catalyzed rearrangement of α-cyclopropyl imines has already been reported but no explanations concerning the mechanism have been given.[11]

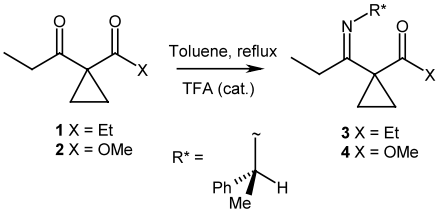
The low stability of imines **3** and **4** prompted us to use the crude compounds in the following step. Phenyl acrylate[12] was chosen as the Michael acceptor since this highly electrophilic olefin is known to lead in situ to 6-ring enamides by loss of a molecule of phenol.[13] Thus, reaction[14] of crude imines **3** and **4** with phenyl acrylate gave respectively the expected dihydropyridin-



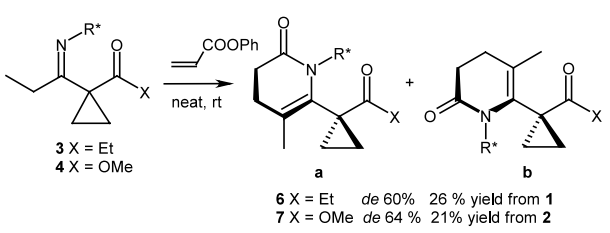
Scheme 3.

2-ones **6** and **7** in 26% and 21% overall yields calculated from starting compounds **1** and **2** (Scheme 4). The partial degradation of the imines **3** an **4**, even during the Michael reaction-azacyclization sequence (liberation of phenol), may explained the moderate overall yields observed. Final products **6** and **7** were in fact obtained as mixtures of diastereomers (diastereomeric excess of 60 and 64%, respectively[15]) which were separated by FC on silica gel and characterized.[16]

As expected, the presence of two diastereomers in the final dihydropyridin-2-ones **6** and **7** is due to the restricted rotation of the exocyclic single bond bearing the cyclopropyl substituent. The rotation barrier is sufficiently high to prevent fast rotation at room temperature since the two different diastereomers of **6** and **7** gave different spectra by ^{1}H NMR analysis. The absolute configurations of major diastereomers of **6** and **7** have not been determined yet. We presumed the diastereomeric ratios in the two reactions (i.e. 80:20 and 82:18) arose from asymmetric induction of the chiral auxiliary during the aza-cyclization step (kinetic ratio) and not from slow equilibration of the final atropisomeric diastereomers (thermodynamic ratio). To prove this, we therefore heated separately each of the pure diastereomers (**6a**, **6b**, **7a**, and **7b**) in refluxing EtOH and in diglyme up to 150°C. In all cases, no traces of the other atropisomeric diastereomer was detected by ^{1}H NMR and GC-MS analyses even after prolonged heating (2 days). These results clearly show that epimerization of the chiral axis by equilibration between diastereomers **a** and **b** can not take place and so we assume that the observed stereoselectivity corresponds to the kinetic ratio of the aza-cyclization. The remarkable high barrier of interconversion between the different diastereomers should reflect the steric hindrance caused by the bulky cyclopropyl moiety. Attempts to improve the stereoselectivity by conducting the reaction at lower temperatures failed since similar *de* were observed at 0°C and the reaction became excessively slow at −20°C.



Scheme 2.

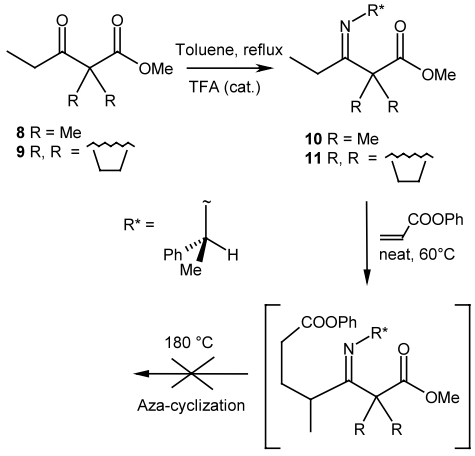


Scheme 4.

Given that the presence of the cyclopropyl group led to moderate yields at each step of the process, we envisaged to replace it by more stable substituents. Thus, a second set of experiments with starting keto-esters **8**[17] and **9**[18] was carried out. Their corresponding crude chiral imines **10** and **11** were obtained under drastic conditions since prolonged heating times (7 d. and 10 d. respectively) were needed to achieve a total conversion of the starting keto-esters. The severe steric hindrance caused by the *gem*-dimethyl or cyclopentyl groups, in comparison of the one caused by the cyclopropyl group, is surely responsible of the low reactivity of the carbonyl group. Imines **10** and **11** were first reacted with phenyl acrylate at room temperature. However, no Michael reaction took place at this temperature. Careful monitoring of the reaction by GC-MS analyses of the reaction mixture has shown that a minimum temperature of 60°C is required for the Michael reaction but that the subsequent aza-cyclization can not occur even at drastic temperatures (180°C) (Scheme 5).

This unexpected result can be rationalized if we consider that during the aza-cyclization step the bulky *gem*-dimethyl or cyclopentyl groups should push away the chiral auxiliary moiety, this latter preventing the approach of the ester chain (Fig. 1).

In conclusion, we have succeeded in the stereoselective synthesis of atropisomeric dihydropyridinones and we have shown that epimerization of the chiral axis can not take place at standard temperatures proving that the observed stereoselectivity is under kinetic control. Moreover, the route developed for the preparation of this new class of atropisomeric compounds relies on an efficient Michael reaction-azacyclization sequence. However, this preliminary study on 6-non-aryl compounds has also shown that the choice of the 6-exo-substituent which generates the atropisomerism is limited. Thus, we focused our interest on 6-aryl dihydropyridinones which revealed to be more versatile and the study concerning their synthesis will be published in an accompanying paper.



Scheme 5.

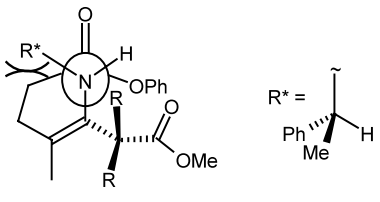


Figure 1.

Acknowledgements

We thank the Laboratoire de Spectrométrie de Masse, (Université de Rouen, Faculté des Sciences, IRCOF, France) for the HMRS analyses.

References

1. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp. 1142–1155.
2. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
3. For a review see: (a) Clayden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *9*, 949–951. For recent leading references on axially chiral anilides see: (b) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130–5131; (c) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Tagushi, T. *J. Org. Chem.* **2000**, *65*, 1108–1114; (d) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033–7040; (e) Hugues, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607–7610. Axially chiral 1-naphtamides: (f) Dai, W.-M.; Yeung, K. K. Y.; Chow, C. W.; Williams, I. D. *Tetrahedron: Asymmetry* **2001**, *12*, 1603–1613; (g) Clayden, J.; Lai, L. W. *Tetrahedron Lett.* **2001**, *42*, 3163–3166; (h) Clayden, J.; Helliwell, M.; McCarty, C.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3232–3249; (i) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, 37, 2899–2902. Axially chiral benzamides: (j) Clayden, J.; Lai, L. W.; Helliwell, M. *Tetrahedron: Asymmetry* **2001**, *12*, 695–698; (k) Clayden, J.; Pink, J. H.; Samreen, A. Y. *Tetrahedron Lett.* **1998**, *39*, 105–108. See also for atropisomeric pyrazinones: (l) Tulinsky, J.; Cheney, B. V.; Mizsak, S. A.; Watt, W.; Han, F.; Dolak, L. A.; Judge, T.; Gammill, R. B. *J. Org. Chem.* **1999**, *64*, 93–100.
4. See Refs 3a,c. Koide, H.; Uemura, M. *Chem. Commun.* **1998**, 2483.
5. See Refs 3a,e,f,g. (a) Chen, Y.; Smith, M. D.; Shimizu, K. D. *Tetrahedron Lett.* **2001**, *42*, 7185–7187; (b) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279–3283.
6. (a) Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795–1812; (b) Jabin, I.; Revial, G.; Pfau, M.; Decroix B.; Netchitaïlo, P. *Org. Lett.* **1999**, *1*, 1901–1904; (c) Revial, G.; Jabin, I.; Pfau, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4975–4983; (d) Jabin, I.; Revial, G.; Monnier-Benoit, N.; Netchitaïlo, P. *J. Org. Chem.* **2001**, *66*, 256–261; (e) Jabin, I.; Netchitaïlo, P. *Tetrahedron Lett.* **2001**, *42*, 7823–7827; (f)

Revial, G.; Jabin, I.; Redolfi, M.; Pfau, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1683–1688; (g) Jabin, I.; Revial, G.; Pfau, M.; Netchitaïlo, P. *Tetrahedron: Asymmetry* **2002**, *13*, 563–567. See also: Benovsky, P.; Stephenson, G. A.; Stille, J. R. *J. Am. Chem. Soc.* **1998**, *120*, 2493–2500; d'Angelo, J.; Cavé, C.; Desmaële, D. *Israel Journal of Chemistry* **1997**, *37*, 81–85.

7. Pure diketone **1** and keto-ester **2** were obtained after FC (EtOAc, cyclohexane) from 3,5-heptanedione and 3-oxo-pentanoic acid methyl ester in 42 and 54% yields, respectively. Reaction conditions: 1,2-dibromoethane (1 equiv.), K_2CO_3 (3 equiv.), refluxing acetone, 4–6 days.
1: see Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S.; Gleiter, R.; Eckert-Maksic, M. *J. Org. Chem. USSR* **1986**, 95–105.
2: colorless oil, EIMS *m/z* (rel int) 156 ($M^{+\cdot}$, 8), 141 (16), 127 (base), 125 (17), 95 (23), 79 (20), 59 (44), 57 (42). IR (film): 1747–1670 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, $J=7.0$ Hz, 3H), 1.38 (s, 4H), 3.80 (q, $J=7.0$ Hz, 2H), 3.67 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.60, 19.05 (2C), 34.71, 35.47, 52.56, 171.9, 206.2.
8. Reaction conditions: azeotropic removal of water by refluxing in toluene in a Dean–Stark apparatus, catalytic amount of TFA, 48 h.
9. **3**: oil, $[\alpha]_D^{20}=-33.5$ (*c* 0.92, EtOH). EIMS *m/z* (rel int) 257 (M^+, 26), 228 (11), 124 (67), 105 (base), 79 (19). IR ($CHCl_3$): 1603 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (t, $J=7.4$ Hz, 3H), 1.15 (t, $J=7.4$ Hz, 3H), 1.55 (d, $J=7.0$ Hz, 3H), 2.28 (q, $J=7.0$ Hz, 2H), 2.63–2.89 (m, 3H), 2.92–3.23 (m, 2H), 3.43 (ddd, $J_1=J_2=J_3=10.4$ Hz, 1H), 4.92 (q, $J=7.0$ Hz, 1H), 7.15–7.42 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.88, 12.83, 17.75, 19.66, 27.20, 33.95, 45.49, 52.09, 105.2, 126.9 (2C), 127.7, 129.0 (2C), 140.9, 166.6, 181.9, 194.9.
10. **5**: EIMS *m/z* (rel int) 255 (M^+, 28), 226 (26), 122 (77), 105 (base). ^1H NMR (200 MHz, $CDCl_3$) δ 1.04 (t, $J=7.0$ Hz, 3H), 1.13 (t, $J=7.0$ Hz, 3H), 1.80 (d, $J=7.0$ Hz, 3H), 2.79 (q, $J=7.0$ Hz, 2H), 2.87-2.94 (m, 2H), 5.39 (q, $J=7.0$ Hz, 1H), 6.55 (d, $J=3.1$ Hz, 1H), 6.60 (d, $J=3.1$ Hz, 1H), 6.93-7.37 (m, 5H).
11. (a) Celerier, J. P.; Haddad, M.; Jacoby, D.; Lhommet, G. *Tetrahedron Lett.* **1987**, *28*, 6597–6600; (b) Grotjahn, D. B.; Volhart, K. P. C. *Synthesis* **1993**, 579–605.
12. Phenyl acrylate was prepared according to the literature: Ahlbretch, A.; Codding, D. W. *J. Am. Chem. Soc.* **1953**, *75*, 984.
13. See Refs 6b,e,g.
14. Reactions conditions: phenyl acrylate (1–2 equiv.), neat, room temperature, 48 h.
15. The *de* were determined by a GC-MS analysis of the crude reaction mixtures and were confirmed by ^1H NMR analyses.
16. **6**: major diastereomer: oil, $[\alpha]_D^{20}=-169.2$ (*c* 0.92, EtOH). EIMS *m/z* (rel int) 311 (M^+, 30), 254 (26), 151 (36), 105 (base), 79 (23). IR (film): 1713, 1556 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, $J=7.0$ Hz, 3H), 1.59–2.21 (m, 5H), 1.65 (d, $J=7.0$ Hz, 3H), 2.15 (s, 3H), 2.26–2.77 (m, 4H), 3.25 (dd, $J_1=9.0$ Hz, $J_2=10.6$ Hz, 1H), 5.77 (q, $J=7.0$ Hz, 1H), 7.20–7.43 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.77, 10.86, 17.46, 31.95, 33.36, 33.71, 33.93, 45.59, 54.47, 62.25, 102.4, 127.7 (2C), 128.1, 128.7 (2C), 138.9, 162.9, 195.8, 205.8. Mol. mass calcd. 311.1885; found 311.1884 (M^+, HRMS). Minor diastereomer: oil, $[\alpha]_D^{20}=-321.6$ (*c* 1.03, EtOH). EIMS *m/z* (rel int) 311 (M^+, 17), 254 (19), 151 (25), 105 (base), 79 (15). IR (film): 1755, 1704, 1556 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (t, $J=7.4$ Hz, 3H), 1.58–2.24 (m, 4H), 1.63 (d, $J=6.3$ Hz, 3H), 1.98 (s, 3H), 2.29–2.55 (m, 3H), 2.69 (dq, $J_1=7.4$ Hz, $J_2=18.8$ Hz, 1H), 3.07 (dd, $J_1\approx J_2\approx 10$ Hz, 1H), 3.20 (ddd, $J_1=6.3$ Hz, $J_2\approx J_3\approx 11$ Hz, 1H), 5.75 (q, $J=7.0$ Hz, 1H), 7.18-7.43 (m, 5H). ^1H NMR (200 MHz, $CDCl_3$) δ 8.04, 10.36, 17.84, 31.75, 32.88, 33.48, 33.96, 45.79, 54.04, 62.22, 102.6, 126.2 (2C), 127.7, 128.9 (2C), 141.2, 163.6, 195.5, 205.8. Mol. mass calcd. 311.1885; found 311.1882 (M^+, HRMS).
7: major diastereomer: oil, $[\alpha]_D^{20}=-64.8$ (*C* 0.26, EtOH). EIMS *m/z* (rel int) 313 ($M^{+\cdot}$, 40), 226 (10), 209 (17), 181 (15), 150 (11), 105 (base), 79 (15). IR (film): 1731, 1556 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (d, $J=6.3$ Hz, 3H), 1.72–1.88 (m, 2H), 2.07 (s, 3H), 2.19 (dd, $J_1=5.5$ Hz, $J_2=12.5$ Hz, 1H), 2.29–2.47 (m, 3H), 2,83 (ddd, $J_1=6.2$ Hz, $J_2\approx J_3\approx 11$ Hz, 1H), 3.24 (dd, $J_1=8.2$ Hz, $J_2=11$ Hz, 1H), 3.49 (s, 3H), 5.69 (q, 7.0 Hz, 1H), 7.18-7.4 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.03, 17.64, 31.53, 33.99, 34.05, 45.66, 52.63, 54.41, 56.48, 102.4, 127.9 (2C), 128.0, 128.7 (2C), 139.6, 162.5, 173.4, 196.8. Mol. mass calcd. 313.1678; found 313.1675 (M^+, HRMS). Minor diastereomer: oil, $[\alpha]_D^{20}=-368.4$ (*c* 1.28, EtOH). EIMS *m/z* (rel int) 313 (M^+, 40), 254 (6), 226 (10), 209 (17), 181 (15), 150 (11), 105 (base), 79 (15). IR (film): 1731 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.58 (d, $J=7.0$ Hz, 3H), 1.71–1.91 (m, 2H), 1.94 (s, 3H), 2.23 (dd, $J_1=5.5$ Hz, $J_2=12.5$ Hz, 1H), 2.31–2.42 (m, 2H), 2.50 (ddd, $J_1=2.3$ Hz, $J_2=4.7$ Hz, $J_3=12.5$ Hz, 1H), 3.01 (dd, $J_1=8.2$ Hz, $J_2=10.1$ Hz, 1H), 3.36 (ddd, $J_1=5.5$ Hz, $J_2\approx J_3\approx 11$ Hz, 1H), 3.71 (s, 3H), 5.68 (q, $J=6.8$ Hz, 1H), 7.15–7.42 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.69, 17.36, 31.42, 34.04, 34.16, 46.09, 52.95, 54.37, 56.56, 102.8, 126.7 (2C), 127.8, 129.1 (2C), 141.3, 162.8, 173.6, 196.5. Mol. mass calcd. 313.1678; found 313.1675 (M^+, HRMS).
17. Pure keto-ester **8** was obtained from 3-oxo-pentanoic acid methyl ester after FC (EtOAc, cyclohexane) in 47% yield. Reaction conditions: MeONa (3 equiv.), MeI (2.7 equiv.), MeOH, rt, 2 days.
8: colorless oil, EIMS *m/z* (rel int) 158 (M^+, 1), 127 (7), 102 (54), 87 (22), 73 (18), 70 (27), 57 (base). IR ($CHCl_3$): 1754–1701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, $J=7.0$ Hz, 3H), 1.23 (s, 4H), 2.35 (q, $J=7.0$ Hz, 2H), 3.59 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.23, 22.14 (2C), 31.26, 52.51, 55.50, 174.4, 208.8.
18. Pure keto-ester **9** was prepared from 3-oxo-pentanoic acid methyl ester after FC (EtOAc, cyclohexane) in 84% yield. Reaction conditions: 1,4-diiodobutane (1.2 equiv.), K_2CO_3 (5 equiv.), DMSO, rt, 24 h.
9: colorless oil, EIMS *m/z* (rel int) 184 (M^+, 1), 128 (base), 96 (23), 87 (28), 67 (42), 57 (99). IR ($CHCl_3$): 1748–1700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (t, $J=7.0$ Hz, 3H), 1.44–1.68 (m, 4H), 1.96–2.11 (m, 4H), 2.36 (q, $J=7.0$ Hz, 2H), 3.64 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.60, 25.83 (2C), 32.27, 33.34 (2C), 52.68, 66.70, 174.4, 207.1.