Fused bicyclic piperidines and dihydropyridines by
dearomatising cyclisation of the enolates of
nicotinyl-substituted esters and ketones

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Full Research Paper

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Abstract
The silyl enol ether derivatives of ketones or esters tethered by a hydrocarbon or ether linkage to the 3-position of a pyridine ring undergo dearomatrising nucleophilic attack on the ring once it is activated (as an acylpyridinium species) by the addition of methyl chloroformate. The bicyclic dihydropyridine products are in some cases unstable, but may be isolated after hydrogenation as fused bicyclic piperidines.

Introduction
Oxidative [1-3] or reductive (nucleophilic) [4-21] dearomatising cyclisation reactions are effective strategies for rapidly building complexity and new reactivity from simple, readily made starting materials. We have used cyclisations of benzamide-stabilised carbanions, for example, to give bicyclic functionalised indolinones as intermediates in the synthesis of the neuroactive amino acids [22-32], while related cyclisations of pyridyl-, nicotinamide- and isonicotinamide-containing carbanions yield related bicyclic dihydropyridines [33,34].

While reactive carbanions derived from allyl or benzyllithiums will undergo dearomatising addition even into relatively electron rich rings [35-38], the scope of the dearomatisation can be extended to much less reactive nucleophiles with a more electron deficient aromatic acceptor [39-41]. Thus enolates of glycine esters 1 carrying isonicotinoyl or nicotinoyl N-substituents cyclise readily to yield bicyclic amino acid derivatives 2 (Scheme 1a for example) [39]. Even greater reactivity towards intramolecular nucleophilic attack is exhibited by isonicotinamides when activated by N-sulfonation [40,41]. For example, the N-furylmethyl isonicotinamide 3 cyclises to the doubly dearomatised bis-spirocyle 4 on treatment with triflic anhydride in the presence of an alcohol [41] (Scheme 1b).

In this paper we report the results of cyclising the enolates of ester and ketones tethered to a nicotinyl nucleus via chains
Scheme 1: Dearomatising cyclisations (a) of enolates; (b) of electron-rich heteroaromatics.

which do not incorporate an amide linkage. The starting materials for these cyclisations do not benefit from the favourable conformational disposition of amides 1 and 3, making the reactions more challenging. Likewise, the products are evidently less stable than those produced by the reactions in Scheme 1a, but nonetheless they allow new, partially saturated “drug-like” heterocyclic systems to be formed.

Results and Discussion
Formation of a carbocyclic ring by dearomatising cyclisation

The study was initiated with the synthesis of the δ-nicotinyl ketone 7 as illustrated in Scheme 2. Ethyl benzoylacetate was alkylated with 3-(3-iodopropyl)pyridine 5 and the product 6 hydrolysed and decarboxylated to yield the pyridine 7 in moderate yield.

We assume, in line with previous results [39], that cyclisation occurs only after the addition of the electrophilic trap (which, precedent suggests, attacks the pyridine lone pair and activates the ring as an acylpyridinium species even in the presence of the lithium enolate). Attempts to use bases with a sodium or potassium counter ion led instead to a high yield of the Claisen product 6 (R = Me), presumably because the sodium and potassium enolates are more reactive than the lithium enolate and compete too well with N-acylation.

Next we extended the reaction to the cyclisation of a δ-nicotinyl butyrate ester 12 encouraged by the observations of Onaka [47], who demonstrated that silyl ketene acetals can be added (in an intermolecular fashion) to electron deficient pyridines in the presence of trimethylsilyl triflate, tetrabutylammonium fluoride or a montmorillonite clay.

The cyclisation precursor was synthesised by using the procedure of Hayashi [48] employing a Horner–Wadsworth–Emmons olefination between nicotinaldehyde and phosphonate 10. The resulting mixture of dienes 11 gave ester 12 after hydrogenation (Scheme 4).
It proved challenging to isolate cleanly the silyl ketene acetal derived from 12, so instead we decided to form and cyclise the silyl derivative in a single pot. Thus, ester 12 was added to LDA at −78 °C, and the enolate quenched with trimethylsilyl chloride. After 15 min methyl chloroformate was added and the solution warmed to room temperature. Complete consumption of starting material (by TLC) was accompanied by the appearance of a single less polar spot (R_f 0.77; EtOAc–petroleum ether 1:1). 1H NMR analysis of the crude product after rapid work-up showed two significant sets of new signals at 6.55–6.80 ppm (2H) and 4.65–5.10 ppm (1H) consistent with the dihydropyridine protons of the expected dearomatised product 14 (Scheme 5). However, in contrast with the clean spectra and dearomatised product 8 derived from ketone 7, duplication of many of the signals in the crude 1H NMR spectrum of 14 suggested the existence of either a mixture of diastereoisomers or rotamers caused by restricted rotation of the carbamate group.

No dihydroprpyridine was isolable from this mixture by flash chromatography, probably due to rapid re-aromatisation. However, immediate hydrogenation at ambient pressure using the conditions developed by Arnott for related 3,4-fused dihydroprpyridines [39] gave 15 in 45% yield after chromatography as an inseparable mixture of two diastereoisomers in a ratio of approximately 6:1. A slightly improved yield of 48% was obtained by the use of an H-cube flow hydrogenation apparatus at 40 bar and 30 °C. Unfortunately, again the lack of crystallinity and the large number of overlapping signals in the 1H NMR spectrum frustrated an unequivocal assignment of the stereochemistry. However, hydrogenation of related fused dihydroprpyridines has always led to cis stereochemistry at the ring junction [32,39].

The consequent expected axial–equatorial relationship between the protons at the ring junction is supported by a coupling constant of 4.2 Hz between these protons in 15 (Figure 1) in the major product diastereoisomer. The corresponding 12.9 Hz coupling to the proton α to the ester group is consistent with adoption of an exo–equatorial orientation by this substituent.

![Figure 1: Coupling constants (Hz) in the major diastereoisomer of 15.](image)

**Formation of a tetrahydrofuran by dearomatising cyclisation**

Encouraged by the successful formation of carbocyclic rings in dearomatising cyclisations of nicotinyl ketones and esters, we moved to extend the reaction to the analogous formation of tetrahydrofuranyl esters by cyclisation of starting materials incorporating an enolate nucleophile and a nicotinyl electrophile tethered through an ether linkage. Alkylation of 3-hydroxy-methylpyridine by t-butyl bromoacetate 17a or bromopropionate 17b suffered from competing N-alkylation but returned acceptable yields of the esters 18a and 18b (Scheme 6). As with 13, we anticipated that the silyl ketene acetal derivatives 19...
would be challenging to isolate, so both starting esters 18a and 18b were treated with LDA and Me$_3$SiCl followed by methyl chloroformate (Scheme 7). As with 14, re-amination was fast and the crude products 19 were therefore hydrogenated at atmospheric pressure to give 20a in up to 32% yield from 18a and 20b in up to 35% yield from 18b. The instability of the two non-isolable intermediates meant however that these yields were not consistently reproducible and yields around 25% were more commonly observed. However, scrupulous avoidance of contact with oxygen before the hydrogenation step improved the yield of 20a to 41%. Attempted cyclisation without formation of the silyl enol ether (i.e. omitting Me$_3$SiCl) led to a complex mixture of products.

![Scheme 7: Dearomatising cyclisation to form tetrahydrofurans.](image)

In both cases the cyclic products were obtained as single diastereoisomers, indicating a diastereoselective cyclisation and a face-selective hydrogenation. An nOe experiment on cyclic ether 20b, irradiating the 7a ring junction proton, showed nOe enhancements of protons 3a, 6 (1H) and 7 (1H) (Figure 2). This result is consistent with a cis-fused ring junction. A lack of conclusive nOes prevented determination of the stereochemistry at the ester-bearing centres of 20a or 20b. However, a similar cyclisation with an amide tether [39] had resulted in an endo-orientated ester substituent, and the stereochemistries of 20 are accordingly shown with the ester orientated endo.

**Conclusion**

Tethered ketone or ester enolate nucleophiles undergo dearomatizing attack on a pyridine ring to yield bicyclic products. Yields are greatest if the enolate is first stabilised as a silyl enol ether, presumably because acylation of the pyridine ring to give the electrophilic acylpyridinium species is cleaner. The bicyclic dihydropyridine products are unstable towards re-amination, but can be isolated in moderate to excellent yield if they are hydrogenated in situ, especially when oxygen is excluded prior to and during the hydrogenation.

**Experimental**

5-Benzoyl-5,6,7,8-tetrahydro-4aH-isoquinoline-2-carboxylic acid methyl ester (8)

Methyl chloroformate (0.056 ml, 0.722 mmol) was added to a solution of 9 (45 mg, 0.144 mmol) and triethylamine (0.02 ml, 0.144 mmol) in dichloromethane (5 ml) at –78 °C. After warming to room temperature, dichloromethane was added (30 ml), and the solution washed with water (3 × 10 ml) and brine (10 ml). The combined aqueous layers were extracted with dichloromethane (10 ml) and the combined organic layers dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to furnish a light yellow oil. The oil was purified by flash column chromatography (SiO$_2$; petroleum ether–EtOAc 9:1) to yield the title compound as a colourless oil (40 mg, 0.135 mmol, 93%); silica gel TLC $R_f$ 0.38 (petroleum ether–EtOAc 4:1); IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$): 1721 (carbamate C=O), 1677 (ketone C=O); $^1$H NMR (500 MHz, CDCl$_3$, $\delta_H$): 7.80 (2H, d, $J = 7.5$ Hz, Ph-H), 7.41 (1H, t, $J = 8.0$ Hz, Ph-H), 7.32 (2H, t, $J = 8.0$ Hz, Ph-H), 6.67 (1H, br, py-H$_2$), 6.54 (1H, br, py-H), 4.60 (2H, br, py-H$_2$) 3.64 (3H, br, OCH$_3$), 3.33 (2H, m, py-H$_4$ and CH), 2.1–1.3 (6H, br-m, CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$, $\delta_C$): 202.9 (ketone C=O), 152.2 (carbamate C=O), 137.3, 133.6, 129.1 and 128.9 (aromatic), 123.4 and 123.0 (py-$C_6$), 120.9 and 119.9 (py-$C_4$), 117.1 and 116.8 (py-$C_3$), 108.1 and 107.7 (py-$C_3$), 60.8 (py-$C_4$), 53.8 and 53.7 (OCH$_3$), 38.0 and 37.8 (CH), 32.5 and 32.4 (CH$_2$), 31.7 and 31.6 (CH$_2$), 27.5 (CH$_2$); CIMS $m/z$ (relative intensity): 298 (100%, M+H$^+$), 238 (40%, M-CO$_2$Me); EIMS $m/z$ (relative intensity): 297 (10%, M$^+$). [Found: M+H$^+$, 298.1436. C$_{18}$H$_{20}$NO$_3$ requires 298.1438].

![Figure 2: Determination of the stereochemistry of 20b. Arrows indicate nuclear Overhauser enhancements.](image)
5-Ethyl 2-methyl octahydroisoquinoline-2,5-(1H) dicarboxylate (15)

n-Butyllithium (0.36 mL of a 1.8 M solution in hexane) was added to a solution of disopropylamine (0.11 mL, 0.75 mmol) in THF (15 mL) at 0 °C and the mixture stirred for 15 min before cooling to −78 °C. A solution of ester 12 (0.104 g, 0.5 mmol) in THF (5 mL) and then trimethylsilyl chloride (0.10 mL, 0.75 mmol) were added using a cannula. The solution was stirred at −78 °C for 15 min, methyl chloroformate (0.19 mL, 2.5 mmol) was added and the solution warmed to room temperature. The solution was rapidly added to a saturated sodium hydrogen carbonate solution (30 mL), extracted with EtOAc (2 × 30 mL), dried (MgSO₄), and concentrated to yield an oil. The crude oil was dissolved in isopropanol (6 mL), and 10% palladium/carbon (0.053 g, 0.05 mmol) was added and the suspension immediately placed under a hydrogen atmosphere. The suspension was warmed to 60 °C for 50 h, filtered through celite and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂; EtOAc–petroleum ether 1:1) to yield the title compound (0.061 g, 0.45%) as a yellow oil which was approximately a 6:1 mixture of diastereomers; Rt (EtOAc–petroleum ether 1:1) 0.45; IR (film) ν max (cm⁻¹): 1730 (C=O ester), 1702 (C=O carbamate).

1H NMR (300 MHz, CDCl₃, δH): 3.95–4.25 (2H, m, 1-H and/or 3-H), 4.13 (2H, q, J = 7.5 Hz, CH₂CH₂₂), 3.68 (3H, s, OMeₙa), 3.65 (OMeₙb), 2.85–3.00 (1H, br m, 1-H or 3-H), 2.63–2.76 (1H, br m, 1-H or 3-H), 2.49 (1H, dt, J = 13.0 Hz, 4.0, 5-H), 2.24 (1H, ap dq, J = 13.0 Hz, 4.0, CH), 1.83 (1H, dt, J = 12.5 Hz, 3.0, CH), 1.65–1.74 (3H, m, CH₂), 1.57 (1H, dd, J = 13.0 Hz, 3.5, CH₂), 1.37–1.51 (2H, m, CH₂), 1.17–1.35 (3H, m, CH₂), 1.25 (3H, t, J = 7.5 Hz, CH₂CH₂₂); 13C NMR (CDCl₃, δC): 174.6 (C=O), 156.7 (C=O), 60.5 (OCH₂), 52.8 (OMe), 49.9 (CH₂), 47.0 (COCH₃), 44.4 (NCH₂), 40.8 (CH), 37.1 (CH), 37.1 (CH₃min), 30.0 (CH₂), 24.2 (CH₂), 24.5 (CH₃min), 24.0 (CH₂), 22.1 (CH₂), 21.5 (CH₃min), 14.6 (CH₂CH₃); MS m/z (relative intensity): 270 (100%, MH⁺); (Found: MH⁺, 270.1699. C₁₄H₂₄O₄ requires MH⁺, 270.1700).

1-tert-Butyl 5-methyl hexahydrofuro[3,4-c]pyridine-1,5(3H)-dicarboxylate (20a)

n-Butyllithium (0.34 mL of a 1.9 M solution in hexane) was added to a solution of disopropylamine (0.11 mL, 0.75 mmol) in THF (10 mL) at 0 °C and stirred for 15 min before cooling to −78 °C. A solution of the ester 18a (0.112 g, 0.55 mmol) in THF (5 mL) was added using a cannula followed by trimethylsilyl chloride (0.10 mL, 0.75 mmol). The solution was then stirred at −78 °C for 45 min, methyl chloroformate (0.19 mL, 2.5 mmol) was added and the solution warmed to room temperature. The solution was rapidly worked-up under a nitrogen atmosphere by addition to saturated sodium hydrogen carbonate solution (30 mL) and extraction with EtOAc (15 mL). 10% Palladium on charcoal (0.053 g, 0.05 mmol) was added and the suspension immediately placed under a hydrogen atmosphere. The suspension was warmed to 45 °C for 18 h, filtered through Celite and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂; EtOAc–petroleum ether 1:4 to 1:1) to yield the title compound (0.058 g, 41%) as white prisms; m.p. 49–51 °C (from EtO); Rt (EtOAc–petroleum ether 1:1) 0.23; IR (film) ν max (cm⁻¹): 1745 (C=O ester), 1705 (C=O carbamate); 1H NMR (300 MHz, CDCl₃, δH): 4.37 (1H, d, J = 5.0 Hz, 1-H), 3.95–4.10 (2H, m, 4-H (1H) and 6-H (1H)), 3.98 (1H, t, J = 8.5 Hz, OCH₂H₆β), 3.79 (1H, t, J = 8.5 Hz, OCH₂H₆α), 3.74 (3H, s, OMe), 3.14–3.24 (1H, m, 4-H), 2.71–2.87 (1H, m, 6-H), 2.44–2.57 (2H, m, 3a-H and 7a-H), 1.50–1.58 (2H, m, 7-H), 1.47 (9H, s, (CH₃)₃); 13C NMR (CDCl₃, δC): 169.9 (C=O), 156.2 (C=O), 82.1 (C(CH₃)₂), 81.3 (1-C), 69.2 (3-C), 52.9 (OMe), 42.6 (2-C), 41.7 (4-C), 39.6 (7a-C), 38.3 (3a-C), 28.4 ((CH₃)₂), 22.2 (7-C); MS m/z (relative intensity): 286 (15%, MH⁺), 230 (100%, MH⁺–(CH₃)₃); (Found: MH⁺, 286.1646. C₁₄H₂₂N₂O₄ requires MH⁺, 286.1649).

Dimethyl 1-methylhexahydrofuro[3,4-c]pyridine-1,5(3H)-dicarboxylate (20b)

n-Butyllithium (0.34 mL of a 1.9 M solution in hexane) was added to a solution of disopropylamine (0.11 mL, 0.75 mmol) in THF (15 mL) at 0 °C and stirred for 20 min before cooling to −78 °C. A solution of the ester 18b (0.098 g, 0.5 mmol) in THF (5 mL) was added using a cannula followed by trimethylsilyl chloride (0.10 mL, 0.75 mmol). The solution was then stirred at −78 °C for 15 min and methyl chloroformate (0.19 mL, 2.5 mmol) was added and the solution warmed to room temperature. The solution was rapidly worked-up by addition of saturated sodium hydrogen carbonate solution (30 mL), extracted with EtOAc (2 × 30 mL), dried (MgSO₄) and evaporated under reduced pressure. The residue was dissolved in propan-2-ol (7 mL), 10% palladium on charcoal (0.053 g, 0.05 mmol) was added and the suspension was immediately placed under a hydrogen atmosphere. The suspension was warmed to 50 °C for 24 h, filtered through celite, washed with EtOAc (5 × 10 mL) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂; EtOAc–petroleum ether 3:1 to 1:1) to yield the title compound (0.033 g, 35%) as a colourless oil; Rt (EtOAc–petroleum ether 1:1) 0.25; IR (film) ν max (cm⁻¹): 1752 (C=O ester), 1702 (C=O carbamate); 1H NMR (300 MHz, CDCl₃, δH): 4.07 (1H, t, J = 8.5 Hz, OCH₂H₆β), 3.81 (1H, t, J = 9.0 Hz, OCH₂H₆α), 3.75–4.02 (2H, m, 4-H and 6-H), 3.75 (3H, s, OMe), 3.24 (1H, br d, J = 12.5 Hz, 4-H or 6-H), 2.79 (1H, t, J = 12.0 Hz, 4-H or 6-H), 2.66 (1H, br s, 3a-H), 2.17–2.27 (1H, m, 7a-H), 1.49–1.64 (2H, m, 7-H), 1.46 (3H, s, (CH₃)₃); 13C NMR (CDCl₃, δC): 174.0 (C=O ester), 156.4 (C=O carbamate), 87.5 (1-C), 69.1 (3-C), 53.0 (OMe), 52.4 (OMe), 45.1 (7a-C), 42.6 (6-C), 41.8 (4-C), 36.9 (3a-C), 28.4 ((CH₃)₂), 22.2 (7-C); MS m/z (relative intensity): 286 (15%, MH⁺), 230 (100%, MH⁺–(CH₃)₃): (Found: MH⁺, 286.1646. C₁₄H₂₂N₂O₄ requires MH⁺, 286.1649).
Supporting Information

Supporting Information File 1
Synthesis and characterisation data of starting materials
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-22-S1.pdf]

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References

1. Zhdanikin, V. V.; Stang, P. J. Chem. Rev. 2006, 108, 5299.
doi:10.1021/cr060332c
2. Vo, N. T.; Face, R. D. M.; O’Yara, F.; Gaunt, M. J. J. Am. Chem. Soc. 2008, 130, 404. doi:10.1021/ja077457u
And references therein.
3. Hamamoto, H.; Anikumar, G.; Hirofumi, T.; Kita, Y. Chem.--Eur. J. 2002, 8, 5377.
doi:10.1002/1521-3765(20021202)8:23<5377::AI2-CHEM5377>3.0.C
4. Dai, M.; Danishefsky, S. J. Heterocycles 2009, 77, 157.
doi:10.3987/COM-08-S(F)6
5. López-Ortiz, F.; Iglesias, M. J.; Fernández, I.; Andujar Sanchez, C. M.; Ruiz-Gómez, G. Chem. Rev. 2007, 107, 1580. doi:10.1021/cr030207i
(see for review).
6. Wang, Z.; Xi, Z. Synlett 2006, 1275. doi:10.1055/s-2006-939083
7. Nevárez, Z.; Woerpel, K. A. J. Org. Chem. 2008, 73, 8113. doi:10.1021/jo0702526
8. Liu, L.; Wang, Z.; Zhao, F.; Xi, Z. J. Org. Chem. 2007, 72, 3484. doi:10.1021/jo070160u
9. Ruiz-Gómez, G.; Iglesias, M. J.; Serrano-Ruiz, M.; García-Granda, S.; Francesc, A.; López-Ortiz, F.; Cuevas, C. J. Org. Chem. 2007, 72, 3790. doi:10.1021/jo070276q
10. Ruiz-Gómez, G.; Francesc, A.; Iglesias, M. J.; López-Ortiz, F.; Cuevas, C.; Serrano-Ruiz, M. Org. Lett. 2008, 10, 3981. doi:10.1021/ol081463g
11. Kumaran, R. S.; Brüggam, I.; Reissig, H.-U. Synlett 2008, 991. doi:10.1055/s-2008-1072512
12. Ovens, C.; Martin, N. G.; Procter, D. J. Org. Lett. 2008, 10, 1441. doi:10.1021/jo0702095
13. Clayden, J.; Kenworthy, M. N.; Hellwell, M. Org. Lett. 2003, 5, 831. doi:10.1021/jo030456x
14. Clayden, J.; Kenworthy, M. N. Org. Lett. 2002, 4, 787. doi:10.1021/jo017262w
15. Clayden, J.; Menet, C. J.; Mansfield, D. J. Org. Lett. 2000, 2, 4229. doi:10.1021/jo000786n
16. Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. Synlett 2001, 302. doi:10.1055/s-2001-10772
17. Ahmed, A.; Clayden, J.; Yasin, S. A. Chem. Commun. 1999, 231. doi:10.1039/a008218i
18. Ahmed, A.; Clayden, J.; Rowley, M. Chem. Commun. 1998, 297. doi:10.1039/a07683e
19. Ahmed, A.; Clayden, J.; Rowley, M. Synlett 1999, 1954. doi:10.1055/s-1999-2977
20. Bragg, R. A.; Clayden, J. Tetrahedron Lett. 1999, 40, 8323. doi:10.1016/S0040-4099(99)01765-7
21. Clayden, J.; Purewal, S.; Hellwell, M.; Mantelli, S. J. Angew. Chem., Int. Ed. 2002, 41, 1049. doi:10.1002/1521-3773(20020315)41:6<1049:AID-AnIE1049>3.0.CO;2-7
22. Clayden, J. Total synthesis of kainoids by dearomatizing anionic cyclisation. In Strategies and Tactics in Organic Synthesis; Harmata, M., Ed.; Academic Press, 2004; Vol. 4, pp 72–96.
23. Clayden, J.; Knowles, F. E.; Baldwin, I. R. J. Am. Chem. Soc. 2005, 127, 2412. doi:10.1021/ja042415g
24. Clayden, J.; Knowles, F. E.; Menet, C. J. Tetrahedron Lett. 2003, 44, 3397. doi:10.1016/S0040-4093(03)00570-7
25. Clayden, J.; Knowles, F. E.; Menet, C. J. Synlett 2003, 1701. doi:10.1055/s-2003-40993
26. Clayden, J.; Menet, C. J.; Tchabanenko, K. Tetrahedron Lett. 2002, 58, 4727. doi:10.1016/S0040-4093(02)00379-4
27. Clayden, J.; Tchabanenko, K. Chem. Commun. 2000, 317. doi:10.1039/a009325g
28. Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. Tetrahedron Lett. 2001, 42, 3407. doi:10.1016/S0040-4093(01)00501-9
29. Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. Tetrahedron Lett. 2001, 42, 3411. doi:10.1016/S0040-4093(01)00502-0
30. Clayden, J.; Menet, C. J.; Mansfield, D. J. Chem. Commun. 2002, 38. doi:10.1039/b109188c
31. Clayden, J.; Kenworthy, M. N. Synthesis 2004, 1721. doi:10.1055/s-2004-829138
32. Clayden, J.; Read, B.; Hedblitch, K. R. Tetrahedron 2005, 61, 5713. doi:10.1016/j.tet.2005.04.003
33. Clayden, J.; Hamilton, S. D.; Mohammed, R. T. Org. Lett. 2005, 7, 3673. doi:10.1021/ol051214u
34. Clayden, J.; Hennecke, U. Org. Lett. 2008, 10, 3567. doi:10.1021/ol801332n
35. Clayden, J.; Turnbull, R.; Pinto, I. Org. Lett. 2004, 6, 609. doi:10.1021/ol0364071
36. Clayden, J.; Turnbull, R.; Hellwell, M.; Pinto, I. Chem. Commun. 2004, 2430. doi:10.1039/b409150g
37. Clayden, J.; Famaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tellow, D. J.; Hillier, I. H.; Vincent, M. A. J. Am. Chem. Soc. 2009, 131, 3410. doi:10.1021/ja088959e
38. Clayden, J.; Dufour, J.; Grainger, D.; Hellwell, M. J. Am. Chem. Soc. 2007, 129, 7488. doi:10.1021/ja071523a
39. Arnott, G.; Clayden, J.; Hamilton, S. D. Org. Lett. 2006, 8, 5325. doi:10.1021/ol061226s
40. Arnott, G.; Brice, H.; Clayden, J.; Blaney, E. Org. Lett. 2008, 10, 3089. doi:10.1021/ol801092a
41. Brice, H.; Clayden, J. Chem. Commun. 2009, 64. doi:10.1039/b902477b
42. Rassou, S.; Gosmini, R.; Mangene, P.; Alexakis, A.; Commerçon, M. Tetrahedron Lett. 1994, 35, 5433. doi:10.1016/S0040-4093(00)73516-0
43. Yamada, S.; Morita, C. J. Am. Chem. Soc. 2002, 124, 8184. doi:10.1021/ja0203317
44. Rudler, H.; Denise, B.; Xu, Y.; Parlier, A.; Vaissermann, J.
   *Eur. J. Org. Chem.* **2005**, *3724*. doi:10.1002/ejoc.200500162

45. Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, *587*. doi:10.1055/s-1995-5007

46. Rudler, H.; Parlier, A.; Sandoval-Chavez, C.; Herson, P.; Daran, J.-C.
   *Angew. Chem., Int. Ed.* **2008**, *47*, 6843. doi:10.1002/anie.200801879

47. Onaka, M.; Ohno, R.; Izumi, Y. *Tetrahedron Lett.* **1989**, *30*, 747.
   doi:10.1016/S0040-4039(01)80299-9

48. Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.;
   Okada, T.; Miyamoto, T.; Taniguchi, K.; Hayashi, M. *J. Med. Chem.*
   **1981**, *24*, 1149. doi:10.1021/jm00142a006

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