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Asymmetric synthesis of 3-prenyl-substituted pyrrolidin-2-ones

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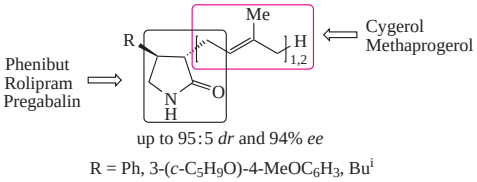
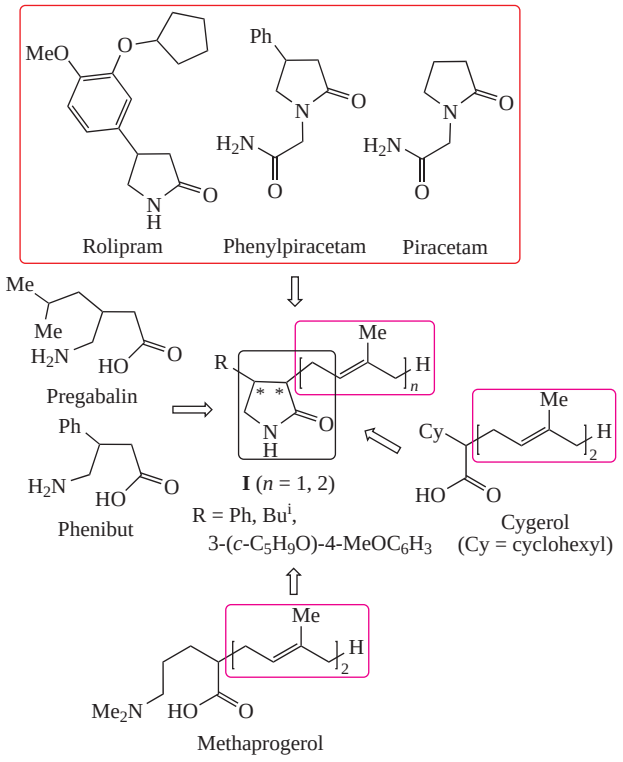
Pharmacology-relevant compounds bearing structural fragments of racetam nootropics, wound-healing acyclic isoprenoids and neurotropic GABA analogues, were enantioselectively (up to 94% *ee*) synthesized from available and inexpensive precursors.



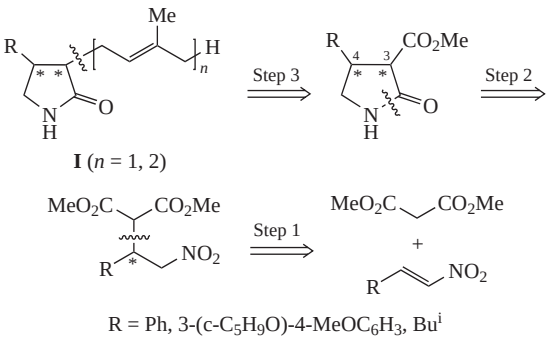
Pyrrolidin-2-one derivatives, cyclic analogues of important natural neurotransmitter γ-aminobutyric acid (GABA), exhibit useful biological activities.[1] Well known piracetam, 2-(2-oxopyrrolidin-1-yl)acetamide, a remedy for treatment of memory disorders and improvement of cognitive functions,[2–4] appeared at pharmaceutical market in 1972 as 'Nootropil'. Afterwards, a number of other nootropic medicines containing the pyrrolidin-2-one fragment (rolipram, pramiracetam, phenylpiracetam, aniracetam, levetiracetam, *etc*.) have been developed,[5–7] which are characterized by higher activity, lower toxicity and minimal side effects.[8,9]

In spite of this positive background, a design of novel, even more efficient, multi-target pyrrolidine-based pharmaceuticals, in particular chiral ones, is still a challenge. These compounds may contain two or more privileged pharmacophoric groups which selectively bind with different cellular receptors (the concept of 'twin drugs').[10,11] We decided to apply this concept to enantioselective synthesis of pyrrolidin-2-one derivatives bearing pharmacophoric prenyl groups along with aromatic or branched aliphatic units. Some of synthetic isoprenoids, in particular geranylacetic acid derivatives cygerol[12] and methaprogerol,[13] are used for treatment of injuries, burns and acute myocardial infarction. Furthermore, methaprogerol and its analogues turned to be promising tracking drugs for cell therapy of various human diseases and artificially induced damages of vital organs or tissues of the laboratory animals with mesenchymal stem cell (MSC) and MSC-derived cardiomyoblasts.[14,15] On the other hand, antiepileptic drug pregabalin,[16] $GABA_B$ receptor agonist phenibut,[17] and antidepressant rolipram[18] contain linear or cyclic (pyrrolidin-2-one) GABA structural units. Proper absolute configuration of stereocenters in these medications is very important as two enantiomers would exhibit different pharmacological activities.[19,20] To the best of our knowledge, just racemic *N*-methyl-3-prenylpyrrolidin-2-one[21] has been synthesized so far. Herein, we report the first enantioselective synthesis of hybrid[22] compounds **I** which are the structural analogues of three types of medications: racetam nootropics, wound-healing acyclic isoprenoids and neurotropic GABA-derived pharmaceuticals (Scheme 1).

According to retro-analysis (Scheme 2), a rational approach towards **I** may include asymmetric addition of malonic ester to corresponding α-nitro olefin (step 1), stereoselective reduction/ring closure tandem reaction of the resulting Michael adduct (step 2) and successive alkylation and decarboxylation reactions (step 3).

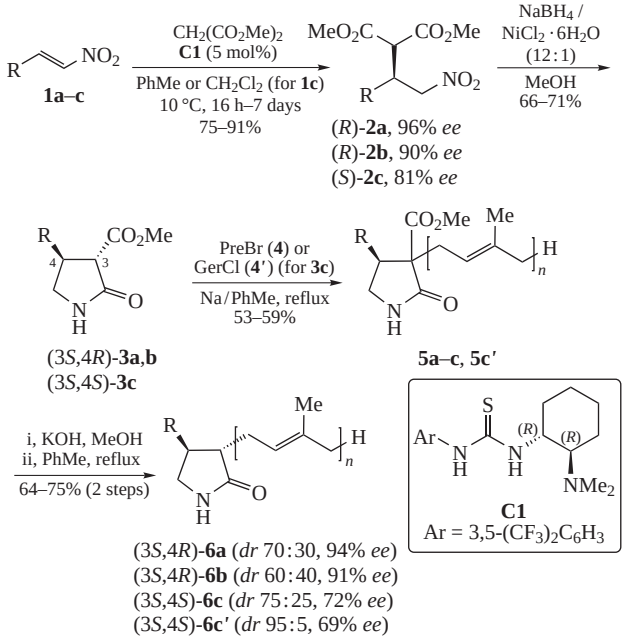


Scheme 1



Scheme 2

Catalytic conjugate addition of malonic and acetoacetic derivatives to α-nitro olefins provides a simple and efficient route to γ-nitro carboxylic acids which are close precursors to valuable analogues of GABA and naturally occurring γ- and δ-lactones.[23–25] Among known (organo)catalysts for asymmetric versions of these reactions, thiourea-derived tertiary amine **C1**, developed by Takemoto,[26,27] is one of the most useful. We applied catalyst **C1** to enantioselective synthesis of nitro esters (*R*)-**2a**,**b** and (*S*)-**2c** from α-nitro olefins **1a**–**c** and dimethyl malonate (Scheme 3).† To attain high efficacy of the reactions, we slightly modified the reported procedures.[26–29] In particular, lowering reaction temperature (10 °C *vs.* room temperature) and catalyst loading (5 mol% *vs*. 10 mol%) improved the enantiomeric enrichment (96% *vs*. 86% *ee*) of product (*R*)-**2a**, though, at the expence of increased reaction time (16 h *vs.* 9 h).[26] To the best of our knowledge, adduct (*R*)-**2b** has not been prepared in the presence of catalyst **C1** so far. Importantly, the reactions allowed one to perform a gram-scale synthesis of nitro esters **2**. Compounds *rac*-**2a**–**c** were synthesized similarly with the use of DABCO[30] or DBU[31] (for *rac*-**2c**) as a base.



Scheme 3

Reductive cyclization of enantiomerically enriched and racemic compounds **2a**–**c** was effectively achieved with $NaBH_4$ (12 equiv.)/$NiCl_2 \cdot 6H_2O$ (1 equiv.) system in methanol[32] to afford corresponding pyrrolidin-2-one derivatives **3a**–**c** as *anti*-diastereomers (according to ^{1}H NMR data and literature[33–35]). Compounds (3*S*,4*R*)-**3a** and (3*S*,4*R*)-**3b** have not been reported so far, though, their enantiomers are known.[33,34]

At first, we treated pyrrolidin-2-ones **3a**–**c** with prenyl bromide **4** or geranyl chloride **4′** in the presence of KOH / Et_3NBnCl phase-transfer catalytic system. However, these reactions were accompanied by polymerization and/or hydrolysis, whatever solvent was used (MeCN, toluene, DMSO or DMF) and these side reactions significantly complicated isolation of products. We succeeded to improve chemoselectivity of the alkylation reactions by performing them with sodium metal in refluxing toluene to furnish the corresponding compounds **5a**–**c** or **5c′** as a mixture of isomers with respect to quaternary carbon atom C-3 in 53–59% isolated yield.

The basic hydrolysis[36]/thermal decarboxylation[29] reactions of compounds **5** furnished the synthesis of pyrrolidin-2-ones **6a**–**c** or **6c′** in 64–75% yields over two steps. According to ^{1}H NMR data (two sets of signals for the CH proton of the prenyl group or for each of two geminal CH_2 protons of the pyrrolidine unit), products **6** consist of two diastereomers in up to 95 : 5 ratio (see Online Supplementary Materials). The single crystal X-ray diffraction study definitely proved *anti*-configuration of substituents in the pyrrolidine ring for the major isomer of *rac*-**6b**, which was isolated from the mixture of diastereomers by column chromatography on silica gel and crystallized from hexane–diethyl ether (Figure 1).‡ By analogy, the same *anti*-configuration was assigned to major isomers of products **6a**, **6c** and **6c′** (H–H coupling constants for protons C^3H and C^4H were uninformative in this case because of significant overlapping between corresponding signals in the mixtures of isomers).

We have not succeeded in obtaining suitable for the X-ray study single crystal of enantiomerically enriched compound **6b**. However, similarity of the *ee* values between key intermediates **2** and major isomers of corresponding compounds **6** strongly testified to the retention of absolute configuration of stereocenter C^4 during alkylation / hydrolysis / decarboxylation reac-

† *Dimethyl (*R*)-2-(2-nitro-1-phenylethyl)malonate (R)-***2a** *and dimethyl (*R*)-2-[1-(3-cyclopentyloxy-4-methoxyphenyl)-2-nitroethyl]malonate (R)-***2b** *(general procedure).* Dimethyl malonate (1.24 g, 9.4 mmol) and catalyst **C1** (100 mg, 5 mol%) were added to a stirred solution of nitro alkene **1a** or **1b** (4.7 mmol) in dry toluene (10 ml). The resulting mixture was stirred at 10 °C under argon for 16 h (for **1a**) or 7 days (for **1b**) and passed through a silica gel pad to remove the catalyst (eluent, EtOAc). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 7 : 1) to afford (*R*)-**2a** or (*R*)-**2b**.

For (*R*)-**2a**: 1.20 g (91%). Colourless solid, mp 59–60 °C (lit.,[30] 60–61 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.58 (s, 3H), 3.78 (s, 3H), 3.88 (d, 1H, *J* 8.9 Hz), 4.23–4.30 (m, 1H), 4.86–4.98 (m, 2H), 7.23–7.38 (m, 5H). According to HPLC [AD-H, *n*-hexane–Pr^{i}OH (7 : 3), 0.7 ml min^{-1}, 220 nm; t_{minor} = 22.7 min; t_{major} = 24.0 min], enantiomeric purity of the product was 96% *ee*.

For (*R*)-**2b**: 1.62 g (87%). Colourless solid, mp 88–90 °C (lit.,[35] 94–96 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.59–1.67 (m, 2H), 1.78–1.99 (m, 6H), 3.59 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.86 (d, ^{1}H, *J* 9.5 Hz), 4.13–4.21 (m, 1H), 4.75–4.88 (m, 3H), 6.74–6.82 (m, 3H). According to HPLC [OJ, *n*-hexane–Pr^{i}OH (7 : 3), 1 ml min^{-1}, 220 nm; t_{major} = 11.4 min; t_{minor} = = 13.4 min], enantiomeric purity of the product was 90% *ee*.

*Dimethyl (*S*)-2-(4-methyl-1-nitropent-2-yl)malonate* (*S*)-**2c**. Dimethyl malonate (0.26 g, 1.9 mmol) and catalyst **C1** (40 mg, 5 mol%) were added to a stirred solution of nitro alkene **1c** (0.25 g, 1.9 mmol) in dry dichloromethane (2 ml). The resulting mixture was stirred at 10 °C under argon for 40 h and passed through a silica gel pad to remove the catalyst (eluent, EtOAc). The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography [silica gel, *n*-hexane–EtOAc (10 : 1)] to afford 0.35 g (75%) of (*S*)-**2c** as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91–0.94 (m, 6H), 1.29–1.35 (m, 2H), 1.61–1.72 (m, 1H), 2.91–3.02 (m, 1H), 3.67 (d, 1H, *J* 5.5 Hz), 3.77 (s, 3H), 3.78 (s, 3H), 4.53 (dd, 1H, *J* 13.4 and 6.4 Hz), 4.71 (dd, 1H, *J* 13.4 and 5.3 Hz).[31,33] According to HPLC [AD-H, *n*-hexane–Pr^{i}OH (98 : 2), 0.7 ml min^{-1}, 210 nm; t_{minor} = 11.0 min; t_{major} = 11.6 min], enantiomeric purity of the product was 81% *ee*.

Full experimental details are given in Online Supplementary Materials.

‡ *X-ray data.* Crystals of *rac*-**6b** ($C_{21}H_{29}NO_3$, *M* = 343.45) are monoclinic, space group $P2_1/n$, at 120 K: a = 12.885(2), b = 6.5217(11) and c = 23.341(4) Å, β = 105.094(4)°, V = 1893.7(6) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.205 g cm^{-3}, μ(MoKα) = 0.80 cm^{-1}, F(000) = 744. Intensities of 18823 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, 2θ < 54°], and 4142 independent reflections (R_{int} = 0.0929) were used in further refinement.

CCDC 1492244 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

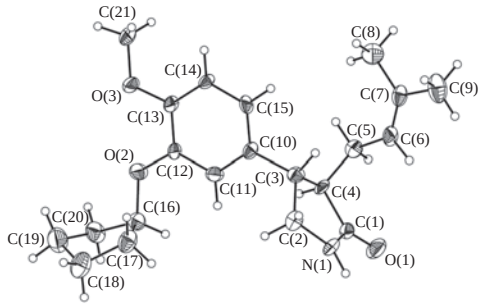
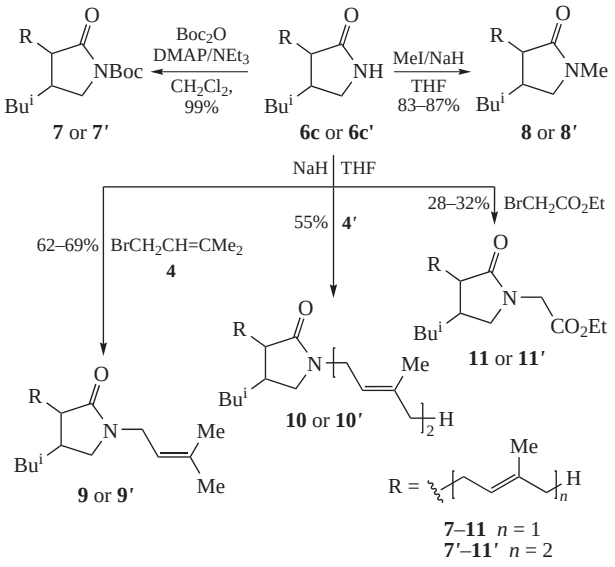


Figure 1 General view of *rac*-**6b** major diastereomer as revealed by X-ray diffraction; atoms are shown as thermal ellipsoids at 50% probability level.

tion sequence. Basing on these results, we assigned (3*S*,4*R*) absolute configuration to major isomers of compounds **6a**,**b** and (3*S*,4*S*) configuration – to major isomers of compounds **6c** and **6c′**. Note that the configuration of stereocenter C^4 in the obtained products **6** corresponds to most active enantiomers of medications phenibut, rolipram and pregabalin.[17,19,20]

A synthetic utility of the developed approach to pharmacology-oriented pyrrolidin-2-one isoprenoid derivatives was further demonstrated by N-functionalization reactions of racemic compounds **6c** and **6c′** to afford novel 1,3,4-trisubstituted pyrrolidones **7**–**11** and **7′**–**11′** (Scheme 4).



Scheme 4

In conclusion, we have developed an efficient approach to enantioselective synthesis of novel pharmacology-relevant prenyl-substituted pyrrolidin-2-ones from available and inexpensive starting compounds (α-nitro olefins, dimethyl malonate, prenyl halides). A favorable combination of privileged pharmacophoric fragments (pyrrolidin-2-one unit, aryl and/or branched alkenyl groups) and proper configuration of key stereocenters allow one to consider the prepared compounds as prospective candidates to further biological studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.11.003.

References

1 A. H. Gouliaev and A. Senning, *Brain Res. Rev*., 1994, **19**, 180.
2 C. Giurgea and M. Salama, *Prog. Neuro-Psychopharmacol*., 1977, **1**, 235.
3 B. Winblad, *CNS Drug Rev.*, 2005, **11**, 169.
4 T. Waegemans, C. R. Wilsher, A. Danniau, S. H. Ferris, A. Kurz and B. Winblad, *Dement. Geriatr. Cogn. Disord*., 2002, **13**, 217.
5 A. G. Malykh and M. R. Sadaie, *Drugs*, 2010, **70**, 287.
6 P. C. R. Wheble, E. S. Sena and M. R. Macleod, *Cerebrovasc. Dis*., 2008, **25**, 5.
7 F. Gualtieri, D. Manetti, M. N. Romanelli and C. Ghelardini, *Curr. Pharm. Des.*, 2002, **8**, 125.
8 J. De Reuck and B. Van Vleymen, *Pharmacopsychiatry*, 1999, **32**, 33.
9 M. Koskiniemi, B. Van Vleymen, L. Hakamies, S. Lamusuo and J. Taalas, *J. Neurol. Neurosurg. Psychiatry*, 1998, **64**, 344.
10 H. Fujii, *Top. Curr. Chem.*, 2011, **299**, 239.
11 J.-M. Contreras and W. Sippl, in *The Practice of Medicinal Chemistry*, 3rd edn., ed. C. G. Wermuth, Academic Press, Amsterdam, 2008, pp. 380–414.
12 (*a*) L. S. Bondar and R. A. Okunev, *British Patent GB 1173419*, 1969 (*Chem. Abstr*., 1970, **72**, 54770f); (*b*) L. S. Bondar and R. A. Okunev, *German Patent DE 1801868*, 1970 (*Chem. Abstr*., 1970, **73**, 34814r); (*c*) L. S. Bondar and R. A. Okunev, *Avtorskoe svidetel'stvo SSSR 333162*, 1972 (*Chem. Abstr*., 1972, **77**, 100910e); (*d*) J. Nichols and G. F. Bulbenko, *German Patent DE 2335067*, 1974 (*Chem. Abstr*., 1976, **80**, 146380x).
13 (*a*) L. S. Bondar and R. A. Okunev, *German Patent DE 2153832*, 1973 (*Chem. Abstr*., 1973, **79**, 42708y); (*b*) L. S. Bondar and R. A. Okunev, *US Patent 3991086*, 1976 (*Chem. Abstr*., 1976, **86**, 105925j); (*c*) L. S. Bondar, R. A. Okunev, L. V. Polezhaev, S. P. Kolchin, L. V. Cherkasova and L. F. Nikolaeva, *US Patent 4495201*, 1985 (*Chem. Abstr*., 1985, **102**, 172652e).
14 B. B. Smirnov, G. V. Kryshtal, A. G. Konopljannikov, S. G. Zlotin and G. M. Zhdankina, *RF Patent RU 2301667*, 2007 (*Chem. Abstr*., 2007, **147**, 110262).
15 G. V. Kryshtal, G. M. Zhdankina, A. G. Konoplyannikov, V. A. Tartakovsky, E. P. Serebryakov, B. B. Smirnov, O. A. Konoplyannikova, E. V. Agaeva and S. G. Zlotin, *Russ. Chem. Bull., Int. Ed*., 2012, **61**, 253 (*Izv. Akad. Nauk, Ser. Khim.*, 2012, 253).
16 K. Hamandi and J. W. Sander, *Seizure*, 2006, **15**, 73.
17 I. Lapin, *CNS Drug Rev*., 2001, **7**, 471.
18 J. Zhu, E. Mix and B. Winblad, *CNS Drug Rev.*, 2001, **7**, 387.
19 F. Ohsawa, M. Yamauchi, H. Nagaso, S. Murakami, J. Baba and A. Sawa, *Jpn. J. Pharmacol*., 1998, **77**, 147.
20 C. P. Taylor, M. G. Vartanian, Y. Po-Wai, C. Bigge, N. Suman-Chauhan and D. R. Hill, *Epilepsy Res*., 1993, **14**, 11.
21 B. Coates, D. J. Montgomery and P. J. Stevenson, *Tetrahedron*, 1994, **50**, 4025.
22 V. P. Ananikov, E. A. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun*., 2015, **25**, 75.
23 O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem*., 2002, **12**, 1877.
24 (*a*) A. Z. Halimehjani, I. N. N. Namboothiri and S. E. Hooshmand, *RSC Adv*., 2014, **4**, 31261; (*b*) A. Z. Halimehjani, I. N. N. Namboothiri and S. E. Hooshmand, *RSC Adv.*, 2014, **4**, 48022; (*c*) A. Z. Halimehjani, I. N. N. Namboothiri and S. E. Hooshmand, *RSC Adv*., 2014, **4**, 51794.
25 A. Yu. Sukhorukov, A. A. Sukhanova and S. G. Zlotin, *Tetrahedron*, 2016, **72**, 6191.
26 T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc*., 2005, **127**, 119.
27 T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc*., 2003, **125**, 12672.
28 M. Hestericova and R. Šebesta, *Tetrahedron*, 2014, **70**, 901.
29 J.-M. Liu, X. Wang, Z.-M. Ge, Q. Sun, T.-M. Cheng and R.-T. Li, *Tetrahedron*, 2011, **67**, 636.
30 P. Jakubec, D. M. Cockfield, M. Helliwell, J. Raftery and D. J. Dixon, *Beilstein J. Org. Chem*., 2012, **8**, 567.
31 L. Thijs, *US Patent 312560 A1*, 2009.
32 F. Li, Y.-Z. Li, Z.-S. Jia, M.-H. Xu, P. Tian and G.-Q. Lin, *Tetrahedron*, 2011, **67**, 10186.
33 H. Y. Bae and C. E. Song, *ACS Catal*., 2015, **5**, 3613.
34 R. Perlikowska, J. Piekielna, M. Mazur, R. Koralewski, J. Olczak, J.-C. do Rego, J. Fichna, J. Modranka, T. Janecki and A. Janecka, *Bioorg. Med. Chem*., 2014, **22**, 4803.
35 P. S. Hynes, P. A. Stupple and D. J. Dixon, *Org. Lett.*, 2008, **10**, 1389.
36 (*a*) A. Padwa and A. T. Price, *J. Org. Chem*., 1998, **63**, 556; (*b*) A. Civitavecchia, G. Martelli, M. Orena and S. Rinaldi, *Amino Acids*, 2014, **46**, 1097.

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