Molecular Diversity

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Efficient Assembly of Iminodicarboxamides by a "Truly" Four-Component Reaction**

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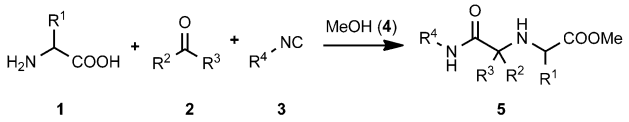
Dedicated to Ivar Ugi

Multicomponent reaction (MCR) technology is now widely recognized for its impact on drug discovery projects and is strongly endorsed by industry as well as academia.[1] Thus, an increasing number of products based on MCRs are marketed or under development. Recent examples include boceprevir,[2] retosiban,[3] and mandipropamide,[4] just to name a few. While the number of described MCRs is enormous, only a small portion has a wide breath within all classes of educts and allows the quasi-infinite variation of all starting materials.[5] The size of the chemical space of the different MCR scaffolds, however, has major implications on the usefulness of the particular MCR. For example, the classical Ugi four-component reactions (U-4CR) allows the simultaneous variation of four very common starting materials (amine, oxo component, carboxylic acid, and isocyanide, which is derived from a primary amine).[6] Thus the number of possible products is very large.[7] In contrast, the three-component reaction of sulfur, carbon monoxide, and an epoxide yielding oxathiolan-2-ones, though synthetically very useful, can yield only a rather limited number of products.[8] Different strategies for the design of molecular complexity using MCR chemistry have been devised.[9] We report herein a novel stereoselective Ugi-type reaction of the four highly variable starting materials: α-amino acid, oxo component, isocyanide, and primary or secondary amine, thus comprising a novel 4-CR.

About 15 years ago Ugi et al. described for the first time the discovery of a novel variant of his reaction (Scheme 1).[10] The reaction was termed a 5-center-4-component reaction (U-5C-4CR) because of the use of bireactive α-amino acids,



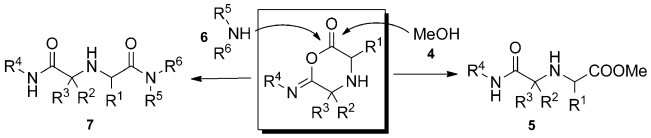
1 2 3 5

Scheme 1. The U-5C-4CR.

oxo components, isocyanides, and an alcohol as a solvent and reactant. The reaction proved to be versatile and several reports document their usefulness.[11] Remarkably, this reaction also lead to the first potent orally available and selective nonpeptide oxytocin antagonist, which is currently undergoing clinical trials for preterm birth.[3,12]

This reaction, however only comprises a MCR where three components show a great variability: the α-amino acid **1**, the oxo-component **2**, and the isocyanide **3**. The variability of the alcohol component **4**, which is also the solvent, is rather restricted to low-molecular-weight liquids such as MeOH and EtOH. The restriction is a result of the poor solubility of the amino acids in other alcohols as well as the reduced nucleophilic reactivity of the alcohols.

The key reaction intermediate is the six-membered α adduct of the α-amino acid, the oxo component, and the isocyanide. This adduct then undergoes nucleophilic attack by the solvent (**4**) methanol to give the linear product **5** (Scheme 2). We envisioned that an N nucleophile, such as



7 6 5

Scheme 2. Proposed key intermediate and the two competing reaction pathways.

the primary or secondary amine **6**, could potentially also work as a nucleophile and successfully compete with the alcohol solvent to attack the six-membered α adduct, thus leading to the iminodicarboxamide derivative **7**. The outcome of the projected reaction however was a priori unclear since the amino acid amine and the external primary or secondary amine could compete for the oxo component and result in different types of Ugi or Passerini products (e.g., by U-5C-4CR, U-4CR, U-3CR, or P-3CR) or mixtures thereof. We hypothesized however, that an intramolecular reaction involving the Schiff base of the bifunctional α-amino acid as

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opposed to an intermolecular reaction of the Schiff base or enamine formed by the additional primary or secondary amine should be more favorable and would preferentially form the cyclic α adduct, thus leading to the new scaffold versus the acyclic α adduct leading to the classic intermolecular Ugi product. Additionally a reaction proceeding by the projected reaction pathway would be of high value since this would represent one of the very few four-component reactions which are truly variable in all components.

To test our MCR hypothesis we first reacted leucine (**1**{7}), 2-fluorobenzaldehyde (**2**{16}), benzyl isocyanide (**3**{1}), and morpholine (**6**{14}) and surprisingly found the expected compound **7**{7,16,1,14} as the major product (see Figure 1 for structures). Extensive optimization of the reaction was performed including a look at the solvent, temperature, microwave versus thermal conditions, reaction time, and catalyst and their influence on different combinations of starting materials. In previous Ugi-type reactions where intramolecular cyclization of the α-adduct occurs, trifluoroethanol (TFE) or similar solvents were advantageously used because of their reduced nucleophilicity.[13] Unexpectedly when TFE was attempted in this reaction it was found to produce a significant amount of the trifluoroethylester **5′** as side product. An optimal solvent mixture was found to be MeOH/H_2O (4:1), which is a compromise in solubility for the different classes of starting materials. As a result of the poor solubility of most amino acids we attempted to speed up the reaction by using microwave conditions (from 60–120 °C for anywhere from 30 min to 2 h). Under these reaction conditions the amino acid completely solubilized in the reaction mixture, however no increase in yield was found. Also as a result of the formation of unwanted side products, and therefore an increased difficulty in separation, the benefit from the time gained by using microwave conditions was outweighed by the amount of extra time spent optimizing separation conditions. Instead the reactions were run at room temperature for three days.

Next we investigated the scope of the reaction by using representative starting materials of each class and synthesizing a library of iminobisamides (Figure 1). Not surprisingly it was found that the identity of the starting materials and their specific combinations played a role in the overall yield and selectivity of the reaction. We successfully used virtually all the natural α-amino acids and some nonnatural ones (**1**), including the hindered **1**{3} or oxidation labile **1**{9} and **1**{16}. It was found that while use of Tyr (**1**{13}) gave the desired product **7**{13,7,9,17}, the use of the *tert*-butyl-protected Tyr **1**{14} gave the product **7**{14,7,9,17} in much better yields (25 % versus 47 %). Similar results were seen for Ser (**1**{5}) and the *tert*-butyl-protected Ser **1**{10} giving the products **7**{5,5,4,3} (23 %) and **7**{10,5,4,3} (40 %), respectively. Therefore α-amino acids with reactive side chains (e.g. Ser, Glu, Asp, Lys) were used in their side-chain-protected form. As oxo components (**2**) we often used symmetrical ketones for the sake of formation of only one stereoisomer, however both aldehydes and ketones worked equally well in this reaction. Cyclic ketones, cyclobutanone (**2**{3}), cyclopentanone (**2**{4}), and cyclohexanone (**2**{5}) worked well in the reaction, while cycloheptanone (**2**{6}) and ketones having a larger ring size

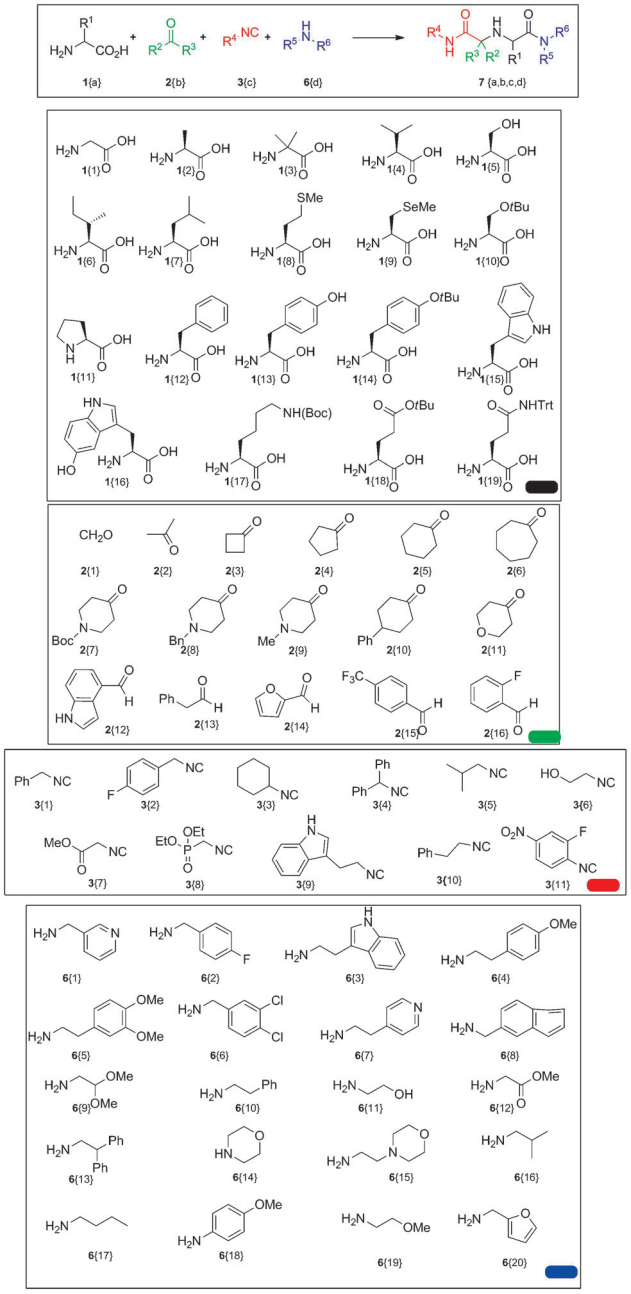


Figure 1. The classes of stating materials as used for the U-4CR reported herein. Boc = *tert*-butoxycarbonyl, Trt = trityl.

reacted with suboptimal yields (e.g., **7**{14,6,5,9}: 23 %). Different isocyanides (**3**) were used, including aromatic, heteroaromatic, aliphatic, and bulky isocyanides and they generally worked well. Primary and secondary amines (**6**) were used as the fourth component, and generally worked well, including functionalized, heterocyclic, aromatic, and heteroaromatic amines. As part of the National Institutes of Health roadmap initiative, a project aimed at addressing roadblocks to research and transforming the way biomedical research is conducted by providing a large and diverse publicly available compound library for the discovery of

molecular probes, we have now synthesized more than 400 compounds based on this reaction.[14] Yields of representative compounds are summarized in Table 1.

Table 1: Products of the U-4CR.

Compound	Yield [%][a]	Compound	Yield [%][a]
7{2,11,9,6}	54	**7**{12,13,5,16}	40
7{9,5,9,10}	50	**7**{7,15,9,19}	34
7{14,7,9,17}	47	**7**{10,5,4,3}	40
7{15,6,1,16}	43	**7**{19,4,2,20}	41
7{1,10,4,17}	42	**7**{12,4,3,13}	38
7{6,3,1,3}	54	**7**{15,4,3,13}	37
7{11,2,4,19}	40	**7**{12,5,9,12}	63
7{15,9,5,10}	51	**7**{17,5,9,18}	62
7{15,2,8,6}	52	**7**{12,5,9,11}	30
7{14,5,7,16}	47	**7**{7,5,3,13}	48
7{10,7,3,7}	41	**7**{7,5,3,3}	46
7{11,2,2,6}	45	**7**{14,14,5,2}	31
7{18,5,1,8}	41	**7**{2,16,2,14}	32
7{6,4,6,5}	33	**7**{2,16,2,15}	28
7{4,5,9,2}	54	**7**{15,2,10,15}	38
7{7,8,4,9}	44	**7**{3,12,5,9}	30
7{6,9,2,1}	51	**7**{1,12,10,4}	41
7{4,8,1,4}	53	**7**{8,8,5,3}	40
7{15,5,4,9}	47	**7**{16,5,4,15}	34

[a] Yields of isolated product after preparative SFC purification (see the Supporting Information).

All reactions were performed on a 0.5 mmol scale and the products were separated into their component diastereoisomers by efficient and fast supercritical fluid carbon dioxide (SFC) technology. The yields in most cases are between 40 and 60% after chromatographic separation and are satisfactory taking into account the complexity of the reaction.

Next we asked the question of the stereochemical integrity of the formed products. Thus all reactions performed were investigated by SFC using a chiral stationary phase (see the Supporting Information). We investigated the influence of the amine component on the integrity of the amino acid stereocenter. We found that primary amines lead to retention of the stereochemical integrity of the amino acid stereocenter, whereas secondary amines lead to partial racemization. This racemization can be rationalized by the higher pK_B value (by 1–2 units) of secondary amines. For example, use of the aldehyde **2**{17} with L-Ala (**1**{2}), benzyl isocyanide (**3**{1}), and morpholine (**6**{14}) leads to the formation of four stereoisomers, which were separated. When 2-morpholinoethylamine **6**{15} was used only two stereoisomers were found. Racemic D,L-Ala in these reactions was used as a control (see Figures 1–4 in the Supporting Information). As a further proof of the structures we solved several compounds in molecular detail using single-crystal X-ray analysis and the structure of

The structure of **7**{15,4,3,13} is shown in Figure 2. An example of a noteworthy combination is phenylacetaldehyde (**2**{13}), Phe (**1**{12}), isobutyl isocyanide (**3**{5}), and isobutyl amine (**6**{16}), the reaction of which leads to C_2- and C_s-symmetric products in a ratio of 6:1 (Figure 1). These otherwise difficult to access C_2-symmetric compounds could

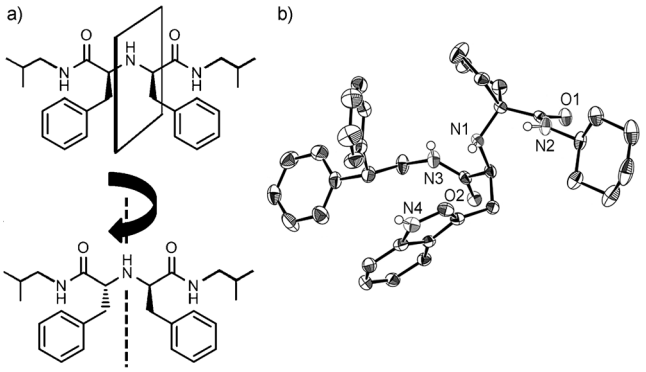
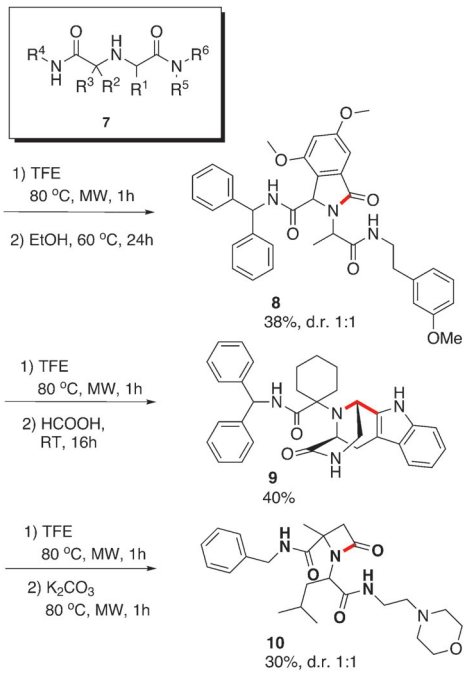


Figure 2. a) Example of C_s- and C_2-symmetrical products conveniently formed by the new U-4CR. b) ORTEP diagram for the compound **7**{15,4,3,13} in the solid state.[22] Thermal ellipsoids are shown at 50% probability.

potentially serve as chiral tridental ligands for catalytic organic transformations.

In another attempt to explore the potential of this four-component reaction we used bifunctional starting materials to cyclize the initially formed Ugi products. Thus we performed cyclizations based on the Pictet–Spengler reaction, and deprotective cyclization. Representative examples (**8–10**) are shown in Scheme 3. Remarkably these cyclizations can be performed without purification of the initial Ugi product.

Iminodicarboxamides are a particular useful class of scaffold and have been reported to have diverse biological activities, including factor Xa,[15] HIV-1 protease,[16] renin,[17] thrombin,[18] and most recently p53/mdm2 inhibition.[19] Our one-pot synthesis towards this scaffold constitutes a major



Scheme 3. Example products resulting from the cyclization of the reported U-4CR (**7**). The newly formed bonds of the cyclization are indicated in red. MW = microwave.

advancement and is superior to reported stepwise sequential or MCR approaches in terms of yield, time, effort, stereochemistry, and breadth of useful starting materials.[20] The scope of the extended U-4CR is large with respect to all investigated starting materials and a very large number of products are theoretically accessible. As MCR chemistry is used more and more in virtual screening tools access to such diverse backbones becomes increasingly significant.[19,21] Towards this end we introduced a freely accessible virtual compound library of approximately five million compounds based on this backbone in the recently published ANCHOR.QUERY software for the discovery of protein–protein interaction antagonists.[19] In conclusion we described a novel and rare case of a U-4CR where all just about all possible combinations of the four classes of starting material can be achieved.

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[1] A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083 – 3135.
[2] S. Venkatraman, S. L. Bogen, A. Arasappan, F. Bennett, K. Chen, E. Jao, Y.-T. Liu, R. Lovey, S. Hendrata, Y. Huang, W. Pan, T. Parekh, P. Pinto, V. Popov, R. Pike, S. Ruan, B. Santhanam, B. Vibulbhan, W. Wu, W. Yang, J. Kong, X. Liang, J. Wong, R. Liu, N. Butkiewicz, R. Chase, A. Hart, S. Agrawal, P. Ingravallo, J. Pichardo, R. Kong, B. Baroudy, B. Malcolm, Z. Guo, A. Prongay, V. Madison, L. Broske, X. Cui, K.-C. Cheng, Y. Hsieh, J.-M. Brisson, D. Prelusky, W. Korfmacher, R. White, S. Bogdanowich-Knipp, A. Pavlovsky, P. Bradley, A. K. Saksena, A. Ganguly, J. Piwinski, V. Girijavallabhan, F. G. Njoroge, *J. Med. Chem.* **2006**, *49*, 6074 – 6086.
[3] J. Liddle, M. J. Allen, A. D. Borthwick, D. P. Brooks, D. E. Davies, R. M. Edwards, A. M. Exall, C. Hamlett, W. R. Irving, A. M. Mason, G. P. McCafferty, F. Nerozzi, S. Peace, J. Philp, D. Pollard, M. A. Pullen, S. S. Shabbir, S. L. Sollis, T. D. Westfall, P. M. Woollard, C. Wu, D. M. B. Hickey, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90 – 94.
[4] C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf, R. Zeun, *Bioorg. Med. Chem. Lett.* **2008**, *16*, 1531 – 1545.
[5] a) M. Passerini, L. Simone, *Gazz. Chim. Ital* **1921**, *51*, 0; b) A. M. Van Leusen, J. Wildeman, O. H. Oldenziel, *J. Org. Chem.* **1977**, *42*, 1153 – 1159; c) A. K. Szardenings, T. S. Burkoth, H. H. Lu, D. W. Tien, D. A. Campbell, *Tetrahedron* **1997**, *53*, 6573 – 6593; d) R. S. Bon, B. van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. de Kanter, C. V. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru, *J. Org. Chem.* **2005**, *70*, 3542 – 3553.
[6] I. Ugi, *Angew. Chem.* **1959**, *71*, 386.
[7] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300 – 3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 – 3210.
[8] Y. Nishiyama, C. Katahira, N. Sonoda, *Tetrahedron Lett.* **2004**, *45*, 8539 – 8540.
[9] a) L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366 – 374; b) A. Dömling, *Curr. Opin. Chem. Biol.* **2000**, *4*, 318 – 323; c) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem.* **2011**, *123*, 6358 – 6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234 – 6246.
[10] A. Demharter, W. Hörl, E. Herdtweck, I. Ugi, *Angew. Chem.* **1996**, *108*, 185 – 187; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 173 – 175.
[11] a) I. Ugi, A. Demharter, W. Hörl, T. Schmid, *Tetrahedron* **1996**, *52*, 11657 – 11664; b) S. J. Park, G. Keum, S. B. Kang, H. Y. Koh, Y. Kim, D. H. Lee, *Tetrahedron Lett.* **1998**, *39*, 7109 – 7112; c) Y. B. Kim, E. H. Choi, G. Keum, S. B. Kang, D. H. Lee, H. Y. Koh, Y. Kim, *Org. Lett.* **2001**, *3*, 4149 – 4152; d) K. Sung, F.-L. Chen, M.-J. Chung, *Mol. Diversity* **2003**, *6*, 213 – 221; e) T. Godet, Y. Bonvin, G. Vincent, D. Merle, A. Thozet, M. A. Ciufolini, *Org. Lett.* **2004**, *6*, 3281 – 3284; f) S. L. Sollis, *J. Org. Chem.* **2005**, *70*, 4735 – 4740; g) I. W. Ku, S. Cho, M. R. Doddareddy, M. S. Jang, G. Keum, J.-H. Lee, B. Y. Chung, Y. Kim, H. Rhim, S. B. Kang, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244 – 5248; h) D. Kadzimirsz, D. Hildebrandt, K. Merz, G. Dyker, *Chem. Commun.* **2006**, 661 – 662.
[12] A. D. Borthwick, J. Liddle, D. E. Davies, A. M. Exall, C. Hamlett, D. M. Hickey, A. M. Mason, I. E. D. Smith, F. Nerozzi, S. Peace, D. Pollard, S. L. Sollis, M. J. Allen, P. M. Woollard, M. A. Pullen, T. D. Westfall, D. J. Stanislaus, *J. Med. Chem.* **2012**, *55*, 783 – 796.
[13] a) B. Beck, S. Srivastava, K. Khoury, E. Herdtweck, A. Domling, *Mol. Diversity* **2010**, *14*, 479 – 491; b) J. Isaacson, Y. Kobayashi, *Angew. Chem.* **2009**, *121*, 1877 – 1880; *Angew. Chem. Int. Ed.* **2009**, *48*, 1845 – 1848.
[14] NIH, Probe Reports from the NIH Molecular Libraries Program (http://www.ncbi.nlm.nih.gov/books/NBK47352/) National Center for Biotechnology Information (US), Bethesda (MD), **2010**.
[15] K. G. Zbinden, L. Anselm, D. W. Banner, J. Benz, F. Blasco, G. Decoret, J. Himber, B. Kuhn, N. Panday, F. Ricklin, P. Risch, D. Schlatter, M. Stahl, S. Thomi, R. Unger, W. Haap, *Eur. J. Med. Chem.* **2009**, *44*, 2787 – 2795.
[16] D. K. Gehlhaar, G. M. Verkhivker, P. A. Rejto, C. J. Sherman, D. B. Fogel, L. J. Fogel, S. T. Freer, *Chem. Biol.* **1995**, *2*, 317 – 324.
[17] C. Jensen, P. Herold, H. R. Brunner, *Nat. Rev. Drug Discovery* **2008**, *7*, 399 – 410.
[18] J. H. Matthews, R. Krishnan, M. J. Costanzo, B. E. Maryanoff, A. Tulinsky, *Biophys. J.* **1996**, *71*, 2830 – 2839.
[19] D. Koes, K. Khoury, Y. Huang, W. Wang, M. Bista, G. M. Popowicz, S. Wolf, T. A. Holak, A. Dömling, C. J. Camacho, *PLoS One* **2012**, *7*, e32839.
[20] a) D. Moderhack, *Justus Liebigs Ann. Chem.* **1973**, *1973*, 359 – 364; b) H. K. Smith, R. P. Beckett, J. M. Clements, S. Doel, S. P. East, S. B. Launchbury, L. M. Pratt, Z. M. Spavold, W. Thomas, R. S. Todd, M. Whittaker, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3595 – 3599; c) J.-y. Chang, E.-k. Shin, H. J. Kim, Y. Kim, Y. S. Park, *Bull Korean Chem. Soc.* **2005**, *26*, 989 – 992.
[21] a) L. Weber, S. Wallbaum, C. Broger, K. Gubernator, *Angew. Chem.* **1995**, *107*, 2452 – 2454; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2280 – 2282; b) M. Shoda, T. Harada, Y. Kogami, R. Tsujita, H. Akashi, H. Kouji, F. L. Stahura, L. Xue, J. Bajorath, *J. Med. Chem.* **2004**, *47*, 4286 – 4290.
[22] CCDC 889602 (**7**{15,4,3,13}) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

