ORGANIC LETTERS

2003
Vol. 5, No. 7
1047−1050

# Short and Diverse Route Toward Complex Natural Product-Like Macrocycles

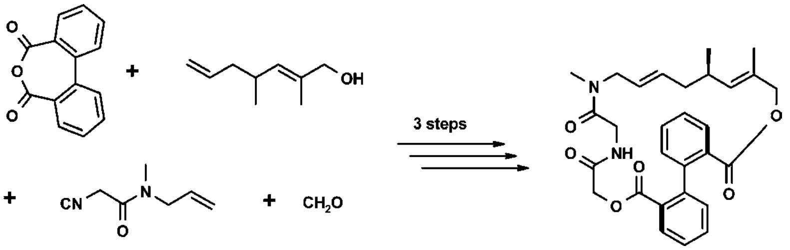
**Barbara Beck,† Gregor Larbig,† Beatrice Mejat,† Marina Magnin-Lachaux,† Anne Picard,† Eberhardt Herdtweck,‡ and Alexander Dömling*,†**

*Morphochem AG, Gmunderstr. 37-37a, 81379 München, Germany, and Anorganisch Chemisches Institut der Technischen Universität München, Lichtenbergstr. 4, 85747 Garching, Germany*

*alexander.doemling@morphochem.de*

Received January 16, 2003

## ABSTRACT



**A general strategy toward macrocyclic compounds using multicomponent reaction (MCR) chemistry, e.g., Passerini and Ugi variants, and ring-closing metathesis (RCM) is introduced. The corresponding bifunctional isocyanides carboxylic acids bearing a terminal olefin are easy to prepare from the corresponding commercially available starting materials. Advantageously, this strategy allows fast access to a diverse conformational space of natural product-like macrocycles and could thus be of interest in the discovery of novel bioactive agents.**

Macrocyclic natural products as opposed to a hypothetical linear structure display a specific three-dimensional binding pattern that is responsible for their biological activity. Typical examples are the antibiotic Vancomycin or the recently described proteasome inhibitors TMC-95, where a specific hydrogen donor/acceptor pattern is displayed toward the target.[1,2] Moreover, the conformational space of bioactive macrocyclic natural products differs substantially from small synthetic drugs. The latter are often small heterocyclic molecules with quite rigid ligands thus allowing only for minute degrees of conformational freedom. For example, the recently introduced nonsteroidal antiinflammatory drug Rofecoxib, a prototypical synthetic small molecule drug, is constituted from a central butenolide moiety with two aromatic ligands. Thus, two rotational degrees of freedom around the connecting butenolide-phenyl moieties and some minor butenolide ring motion are possible. The solution and target-bound conformations are identical in a first approximation.

On the other hand, it is well-known that macrocyclic natural products allow for many more conformational stages.[3] The macrocyclic antibiotic Erythromycin, for example, a 14-membered lactone, is composed of a hydrophilic and a

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† Morphochem AG.

‡ Anorganisch Chemisches Institut der Technischen Universität München.

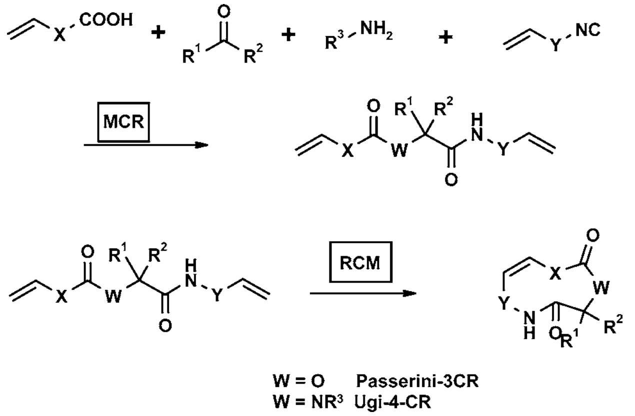
(1) For recent Vancomycin reviews, see: (a) Evans, D. A.; DeVries, K. M. in *Glycopeptide Antibiotics*; Nagarajan, R., Ed.: Marcel Dekker: New York 1994; pp 63. (b) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096.

(2) (a) Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **2000,** *53*, 105. (b) Groll, M.; Koguchi, Y.; Huber, R.; Kohno, J. *J. Mol. Biol.* **2001**, *311*, 543. (c) Renner, C.; Huber, R.; Moroder, L. *Angew. Chem., Int. Ed.* **2002,** *41*, 780.

(3) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.

10.1021/ol034077e CCC: $25.00

**Scheme 1**



hydrophobic site. The preferred solution-phase conformation[4] is quite different from the target-bound conformation in the ribosome and from the assumed transport conformation through the lipid bilayer membrane of the cell.[5]

Thus, it was speculated that, on average, natural products have a much higher propensity to afford biological activity than synthetic products.[6] This was partially related to the larger diversity of chemical and conformational space of natural products. Unfortunately, macrocyclic natural products are often not easily amenable to derivatization, because of a lack of accessibility either by synthesis or fermentation. The more complex natural products are often only available by a lengthy and linear divergent synthetic route.

How can one exploit and take advantage of a much larger conformational space similar to macrocyclic natural products, without being compromised by the few available natural compounds and their often very complex chemistry?[7]

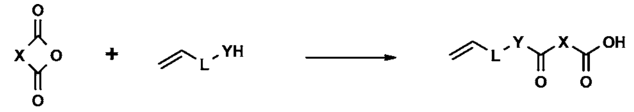
Herein, we would like to introduce a concept that allows rapid access to macrocyclic natural product-like compounds using MCR and RCM chemistries.

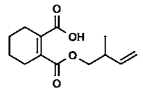
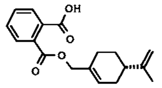
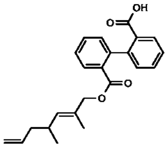
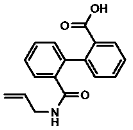
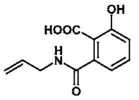
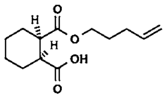
Isocyanide-based multicomponent reactions (MCRs) are an emerging new technology platform useful in drug discovery.[8] They have the invaluable advantages of allowing one-pot, fast, but on the other hand also highly versatile access toward a variety of different and highly relevant organic-chemical scaffolds.[9] Thus, they are easily adaptable to automation and allow the search for useful compounds in very large chemical spaces.[10] Bifunctional starting materials especially promise to open avenues toward novel scaffolds.[11] On the other hand, metathesis of olefins is a very popular and broadly applicable synthetic method toward a plethora of novel compounds useful in organic chemistry.[12] Two bifunctional starting materials with one terminal olefinic bond introduced as starting materials in an MCR thus provide the possibility for a subsequent RCM (Scheme 1). Thus, the combination of the MCR chemistry with ring-closing metathesis appeared to be quite a promising approach toward natural product-like compounds and worth exploiting.[13,14] We would like to focus here on Ugi- and Passerini-type MCRs. From the multiple possibilities for producing macrocycles by MCR/RCM, we focus in this communication on olefin-bearing isocyanides and carboxylic acids.

However, the availability of commercial starting materials useful for this strategy is limited. Therefore, we introduced a general method for the synthesis of such bifunctional olefinic compounds relying on commercially available starting materials.

Olefin-bearing carboxylic acids are sparsely available.[15] However, they are easily accessible in a great variety by the reaction of nucleophiles bearing a double bond with carboxylic acid anhydrides. Both starting materials are abundant from commercial vendors. The reaction between carboxylic acid anhydrides and either alcohols or amines toward $\omega$-olefin carboxylic acids proceeds well in THF in the presence of DMAP mostly in good to excellent yields. Thus, these already quite complex and useful starting materials for MCRs can be synthesized on a multigram scale (Table 1).

**Table 1.** Synthesis of $\omega$-Olefinic Carboxylic Acids



| no | | yield % | no | | yield % |
|---|---|---|---|---|---|
| 1 |  | 90 | 4 |  | 80 |
| 2 |  | 95 | 5 |  | 81 |
| 3 |  | 64[a] | 6 |  | 86 |

[a] Isolated as a mixture of regioisomers.

The following three different strategies for the synthesis of olefin-bearing isocyanides were elaborated. The first strategy involves the potassium salt of isocyano acetic acid,[16] which can be converted to the corresponding esters either

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(4) (a) Bertho, G.; Ladam, P.; Gharbi-Benarous, J.; Delaforge, M.; Girault, J. P. *Int. J. Biol. Macromol.* **1998**, *22*, 103. (b) Bertho, G.; Gharbi-Benarous, J.; Delaforge, M.; Girault, J. P. *Bioorg. Med. Chem.* **1998**, *6*, 209. (c) Steinmetz, W. E.; Bersch, R.; Towson, J.; Pesiri, D. *J. Med. Chem.* **1992**, *25*, 4842. (d) Gharbi-Benarous, J.; Delaforge, M.; Jankowski, C. K.; Girault, J. P. *J. Med. Chem.* **1991**, *34*, 1117.

(5) Schlüntzen, F.; Zarlvach, R.; Harms, J.; Bashan, A.; Tocijl, A.; Albrecht, R.; Yonath, A.; Franceschl, F. *Nature* **2001** *413*, 814.

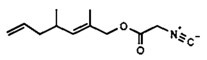
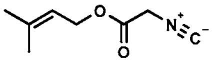
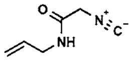
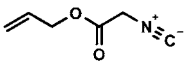
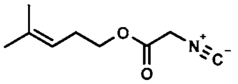
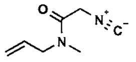
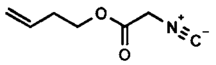
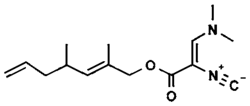
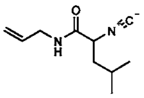
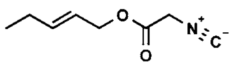
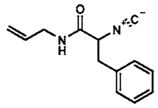
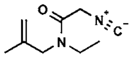
(6) Schreiber, S. L. *Science* **2001**, *287*, 1969.

(7) For a short sequence towards natural-product-like macrocycles: Gagnon, R.; Dory, Y. L.; Deslongchamps, P. *Tetrahedron Lett.* **2000**, *41*, 4751 and references therein.

(8) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmidtt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

(9) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000,** *39*, 3168.

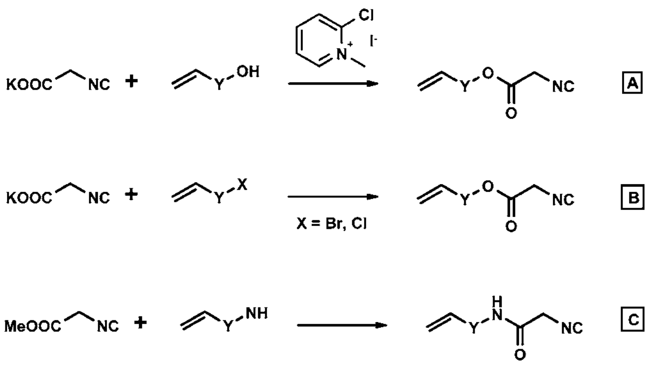
**Table 2.** Prepared *ω*-Olefin Isocyanides

| no | | yield % | no | | yield % | no | | yield % |
|---|---|---|---|---|---|---|---|---|
| 7 |  | 92<br>A | 11 |  | 32<br>B | 15 |  | 95<br>C |
| 8 |  | 55<br>B | 12 |  | 20<br>B | 16 |  | 83<br>C |
| 9 |  | 45<br>B | 13 |  | 21<br>A[a] | 17 |  | 10<br>C |
| 10 |  | 52<br>A | 14 |  | 40<br>C | 18 |  | 42<br>C |

[a] Compound **7** was transformed to **13** by treatment with *N,N*-dimethylformamide dimethylacetal (analogously to: Kolb, J.; Beck, B.; Dömling, A. *Tetrahedron Lett*. **2002**, *43*, 6897.).

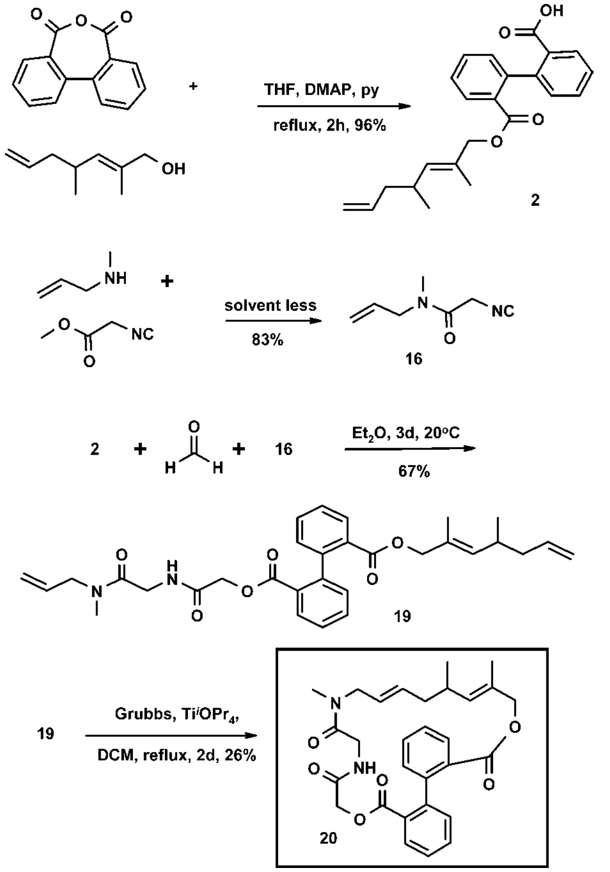
by the use of Mukayama's method[17] employing 2-chloro-1-methylpyridinium iodide or simply by esterfication[18] with the corresponding olefinic halide. In both methods, the corresponding products can be conveniently purified by distillation.

**Scheme 2.** Three Methods for the Synthesis of Olefinic Isocyanides



It is well-known that isocyano acetic acid methyl or ethyl ester reacts with primary or secondary amines in good to excellent yields toward the corresponding amides (Table 2).[19] With this general method, a variety of olefinic isocyanides are easily accessible on a preparative multigram scale (Scheme 3).

**Scheme 3**



Having access to a diversity of olefins bearing isocyanides and carboxylic acids, we then explored the MCR of these quite complex starting materials and their final RCM toward macrocycles.

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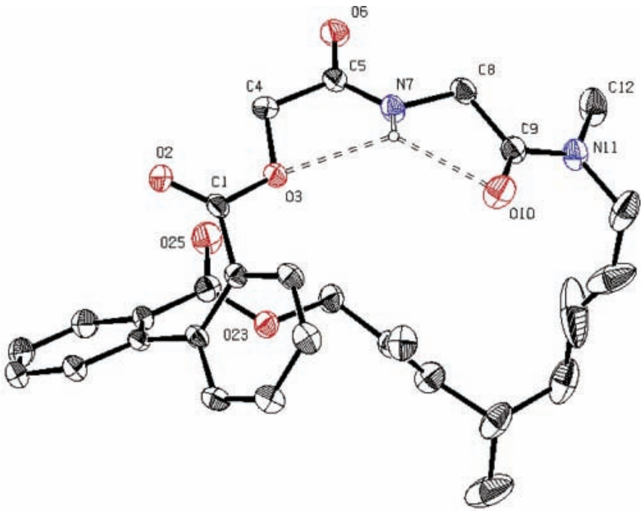
(10) Number of stable compounds below 500 Dalton built from the atoms, C, N, O, H, S, F, Cl, Br, and P has been judged to be in excess of $10^{63}$ (Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Res. Rev.* **1996**, *16*, 3). Very large search spaces therefore are of a similar order of magnitude. All known traditional two-component reactions can only afford much smaller numbers. As early as 1959, Ivar Ugi noticed (Ugi, I., et al. *Chem. Ber.* **1961**, *94*, 734.) that, "If, for example, 40 each of the different components are reacted with one another, the result is $40^4 = 2\,560\,000$ reaction products". With today's commercial availability of several hundred isocyanides (e.g., www.priaton.de) and the broad accessibility of the other functional groups of isocyanide-based MCRs, it is clear that only this reaction type can theoretically cover such large chemical spaces.

(11) (a) Tempest, P.; Ma, V.; Thomas, S.; Hua, Z.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett*. **2001**, *42*, 4959. (b) Hulme, C.; Tang, S.-Y.; Burns, C. J.; Morize, I.; Labaudiniere, R.; *J. Org. Chem.* **1998**, *63*, 8021.

(12) For recent reviews on olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem*. **1998**, *133*, 29.

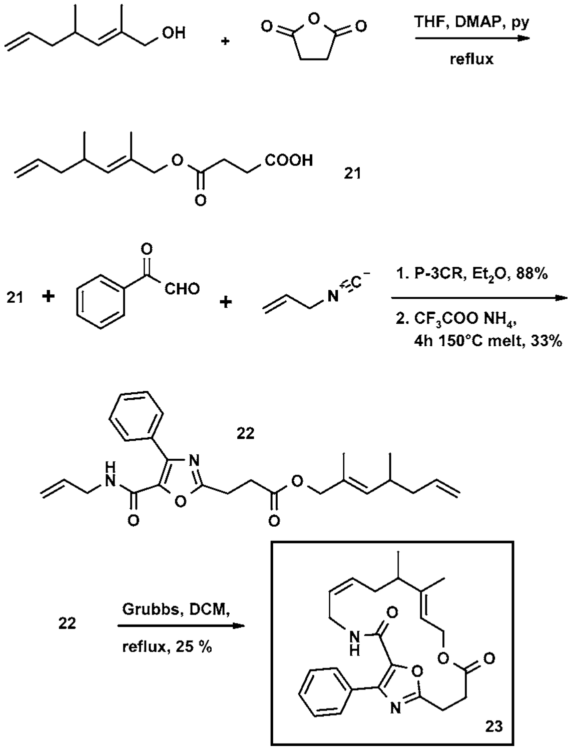
**Scheme 4.** X-ray Crystal Structure Determination of Compound **20**



Carboxylic acid **2** with a terminal olefinic group can be obtained in almost quantitative yield from the commercially available biphenyl carboxylic acid anhydride and the corresponding alcohol. Passerini reaction of **2** with paraformaldehyde and isocyanide **16** affords **19** in 67% yield. Final RCM using Grubbs catalyst under refluxing conditions in DCM yields the 22-membered macrocycle **20**.

Compound **20** can serve as an illustration of the novel concept using MCR/RCM to generate complex natural product-like macrocycles. Compound **20** can be synthesized in only four steps by the following sequence: isocyanide synthesis, ring-opening of the anhydride, Passerini reaction, and RCM, starting from commercially available starting materials in an acceptable 14% overall yield. Compound **20** is a 22-membered macrocycle containing two stereoelements, an asymmetric carbon and an atropisomerism exemplified in the biaryl moiety. In the crystal, the macrocycle is rigidified by two intramolecular hydrogen bonds as revealed by an X-ray structure determination (Scheme 3).[20] Thus, the amide-*H* of N-7 acts as a multiple hydrogen donor toward the adjacent ester-O-3 and the amide-O-10 forming two annealed five-membered rings. The ester-carbonyl-O-X of another molecule acts as a fourth intermolecular hydrogen acceptor for N-7-*H*. Overall, the hydrogen is in a pseudo-tetrahedral coordination sphere.

**Scheme 5**



As a second illustration of the MCR−RCM concept, the synthesis of the 17-membered oxazole containing macrocycle **23** is described. Reacting succinic acid anhydride with commercially available alcohol yields *ω*-olefin carboxylic acid **21**. Passerini reaction of **21** with allyl isocyanide and a glyoxal and the subsequent ring closure to the oxazole[21] affords **22** in 33% yield. RCM of the terminal bisolefin assembles the macrocycle in only four steps and 7% overall yield (Scheme 5).

Efforts in our laboratories are currently underway to transfer this reaction to the solid phase and exploit these reactions in drug discovery as well as in natural product synthesis.

**Acknowledgment.** This work is dedicated to Luis Moroder on the occasion of his 62nd birthday. This work was partially founded by the EU project COMBIOCAT: EC Framework program 5, QLRT-2000-00160.

**Supporting Information Available:** Details for the preparation of the mentioned compounds, including $^1$H and $^{13}$C spectral data and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034077E

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(13) Combination of MCR and metathesis towards small heterocyclic compounds has been described: (a) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851. (b) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189. (c) Lee, D.; Sello, J. K.; Schreiber, S.-L. *Org. Lett.* **2000**, 2, 709.

(14) For other examples of macrocyles by isocyanide-based MCR, see: (a) Failli, A.; Immer, H.; Götz, M. *Can. J. Chem.* **1997**, *57*, 3257. (b) Schmidt, U.; Weinbrenner, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1003. (c) Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355. (d) Owens, T. D.; Araldi, G.-L.; Nutt, R. F.; Semple, J. E. *Tetrahedron Lett.* **2001**, *42*, 6271. (e) Lobrégat, V.; Alcaraz, G.; Bienaymé, H.; Vaultier, M. *Chem. Commun.* **2001**, 817. (f) Cristau, P.; Vors, J.-P.; Zhu, J. *Org. Lett.* **2001**, *3*, 4079.

(15) (a) Ito, Y.; Higuchi, N.; Murakami, M. *Tetrahedron Lett.* **1988**, *40*, 5151. (b) Garrido, M. A.; Herrera, A. J.; Johannsen, J.; Beck, J.; Godet, T.; Vrettou, M.; White, A. J. P.; Williams, D. J. *Tetrahedron Lett.* **2002**, *43*, 1751.

(16) Hoppe, I.; Schöllkopf, U. *Chem. Ber.* **1976**, *109*, 482.

(17) Ito, Y.; Murakami, M. *Tetrahedron Lett.* **1988**, *29*, 5151.

(18) Suzuki, M.; Nunami, K.-I.; Matsumoto, K.; Yoneda, N.; Kasuga, O.; Yoshida, H.; Yamaguchi, T. *Chem. Pharm. Bull.* **1980,** *28*, 2374.

(19) Chupp, J.; Leschinsky, K. *J. Heterocycl. Chem.* **1980**, *17*, 705.

(20) See Supporting Information for data of X-ray single-crystal structure determination of compound **20**.

(21) Claiborne, F. C.; Liverton, N. J.; Nguyen, K. T. *Tetrahedron Lett.* **1998**, *39*. 8939.