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Expeditious Divergent Synthetic Approach to Polycyclic Terpene-Like Molecules

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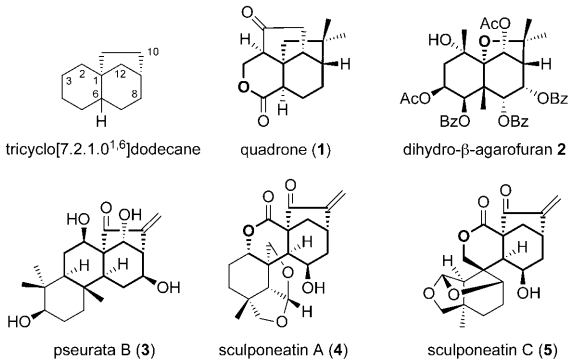
Small-molecule natural products (SMNPs) are privileged molecular architectures for the discovery of new therapeutic agents. The importance of natural product based drugs in the human pharmacopoeia is considerable, with only a very small proportion of true unmodified natural products.[1] The integration of natural-product-inspired compounds into medicinal chemistry and chemical biology research programs can only be realized successfully if efficient synthetic methods are available to solve the problem of compound supply and give a rapid access to focused small collections of these compounds.[2] Sequential multiple bond-forming transformations (MBFTs),[3] which include consecutive and domino reactions, have already proven well suited for this purpose, allowing simplification of synthetic schemes.[4]

The tricyclo[7.2.1.0^{1,6}]dodecane ring system, often incorporating a heteroatom, is found in several classes of terpenoids, which generally possess important biological activities (see compounds **1**–**5**).[5] Previous analyses of the various biological activities observed in these classes of terpenoids have allowed the identification of several key structural factors required for good activity and that are specific to each class of products.[5] However, overall the most essential structural factor common to compounds **1–5** and their congeners might be the rigid tricyclic [7.2.1.0^{1,6}] dodecane framework, which allows the positioning of different functional and binding groups of the molecules in well-defined topologies, suitable for good interactions with proteins.

In this respect, synthetic methods for the stereoselective preparation of the tricyclo[7.2.1.0^{1,6}]dodecane scaffold are highly desirable and methodologies versatile enough to allow the efficient synthesis of both diastereomers (controlled relative configuration at C6)[6] of the substituted and functionalized target ring system in only a few chemical operations would be of value. Herein, we report a protection-free stereodivergent approach for the expeditious synthesis of 3-oxa- and 3-aza-tricyclo[7.2.1.0^{1,6}]dodecane compounds based on the synergic combination of MBFTs recently developed in our laboratory. This methodology has been extended to the synthesis of the 9-oxa-bicyclo[5.4.0]undecane ring system, another scaffold found in naturally occurring terpenes.



We decided to target molecules of type **6** because of their structural similarity to natural products **1**–**5**. Indeed, compounds of type **6** exhibit the same tricyclic ring system with incorporation of a heteroatom in the 3-position as found in compounds **4** and **5**, but also in compounds **1** and **2**, although at a different position of the ring system. Compounds of type **6** also incorporate R (R = alkyl) substituent(s) at C10 as found in all compounds **1–5** and their congeners, and, importantly, compounds **6** also exhibit three oxidized positions, with carbon atoms C2, C8 and C12 bonded to an oxygen atom as in natural products **2** and **3**, and in part in **4** and **5**. Our retrosynthetic analysis for compounds of type **6** (Scheme 1) has led to a strategy involving just two reactions; an intramolecular domino Michael–aldol reaction from the 1,3-dicarbonyl compound **7**, which should

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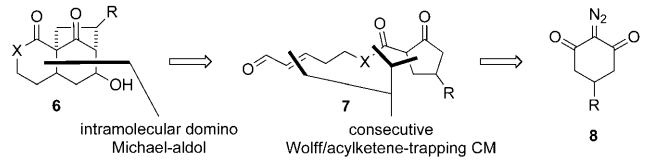
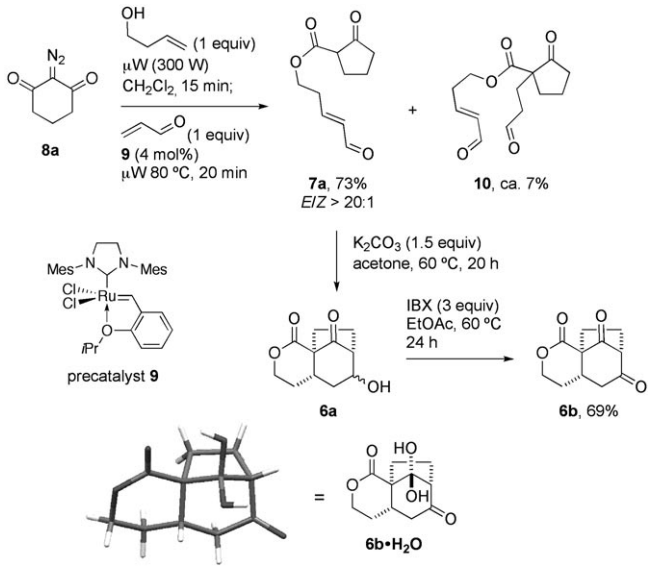


Scheme 1. Retrosynthetic analysis.

be obtained by a consecutive reaction involving a Wolff rearrangement/acylketene-trapping cross metathesis (CM) sequence from the simple diazo compounds **8**.

We first examined the preparation of compounds of type **6** in the 3-oxa series (X = O). According to the planned synthetic scheme, we attempted the preparation of compound **7a** from 2-diazo-1,3-cyclohexanedione (**8a**) by an innovative consecutive reaction.[7] Thus, a microwave-assisted Wolff rearrangement of **8a** in the presence of homoallyl alcohol (1 equiv) generated the corresponding ring-contracted β-ketoester,[8] which was then directly treated with acrolein and the Grubbs–Hoveyda precatalyst **9** under microwave irradiation[9] to efficiently produce **7a** in a single consecutive reaction (Scheme 2). In early trials, the reaction was complicated

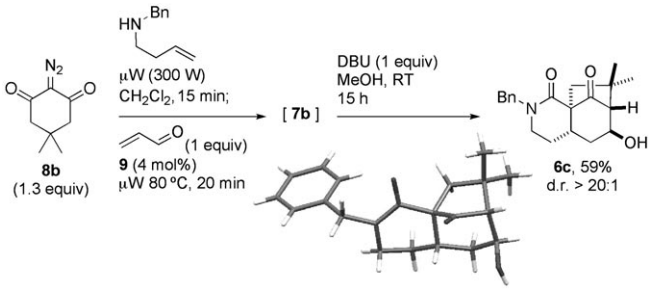


Scheme 2. Synthesis of 3-oxa-tricyclo[7.2.1.0^{1,6}]dodecane compounds. Mes = mesityl; IBX = 2-iodoxybenzoic acid.

by the domino formation of the undesired intermolecular Michael addition product **10**, and no spiro product resulting from the intramolecular Michael addition of **7a** could be detected. In this reaction, formation of compound **10** is possibly catalyzed by the Lewis acid properties of the ruthenium species generated during the metathesis catalytic cycle or their degradation products.[10]

With **7a** optimized, we turned our attention to the key intramolecular domino Michael–aldol step. Related intermolecular domino Michael–aldol reactions have been well studied for the preparation of bicyclo[3.2.1]octane ring systems,[11] and it was rapidly found that K_2CO_3 in acetone gave the desired tricyclic product **6a** efficiently as a mixture of two diastereomers (>90% yield, from crude NMR data). However, compound **6a** partially decomposed during silica gel chromatography and only 55% (diastereomeric ratio (d.r.) = 1:1) of product could be isolated. Thus, the diastereomeric mixture of crude hydroxy ketone **6a** was directly oxidized with 2-iodoxybenzoic acid (IBX) in ethyl acetate[12] to afford the diastereomerically pure diketone **6b** (in 69% overall, from **7a**), which confirmed the excellent diastereoselectivity of the Michael addition. Upon storage, the bridging ketone in **6b** was hydrated, and the resulting crystallized material **6b·H$_2$O** was analyzed by X-ray diffraction techniques[13] to give the structures of **6a** and **6b** (Scheme 2).

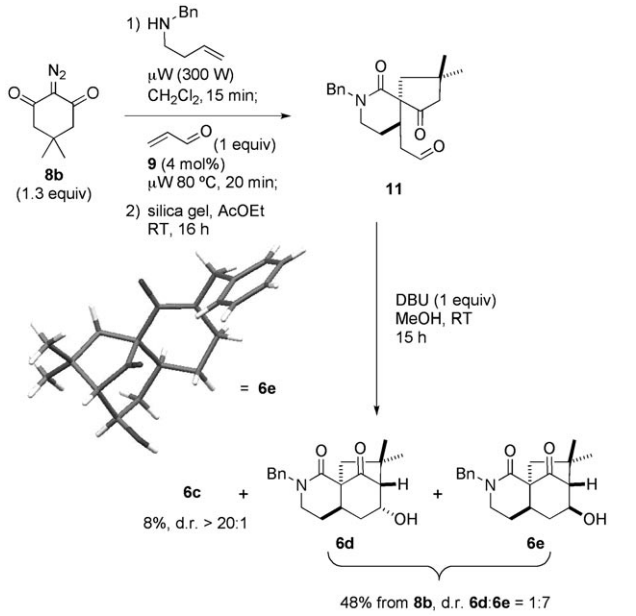
A similar strategy was used in the 3-aza series for the expeditious synthesis of compound **6c** (Scheme 3). The Wolff



Scheme 3. Synthesis of a 3-aza-tricyclo[7.2.1.0^{1,6}]dodecane compound. Bn = benzyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

rearrangement/acylketene-trapping CM consecutive reaction was performed as before, but with a slight excess of diazo compound **8b** to consume the residual secondary amine, which would deactivate the CM catalyst.[14] The resulting product mixture of **7b** was simply concentrated, diluted in methanol, and treated with DBU to promote the intramolecular domino Michael–aldol reaction, allowing the isolation of **6c** as a single diastereomer in 59% yield from **8b**, as confirmed by X-ray diffraction.[13] A remarkable feature of this synthetic sequence is that compound **6c**, which exhibits a 3-aza-tricyclo[7.2.1.0^{1,6}]dodecane framework with four controlled stereogenic centers, is obtained by a one-pot combination of two MBFTs: a consecutive reaction followed by a domino reaction in a practical one-pot operation.[3]

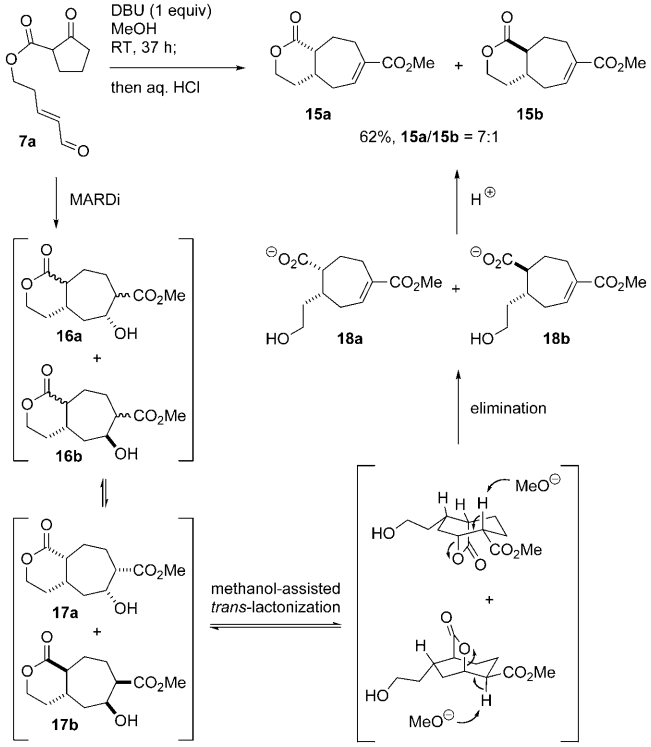
Our early attempts to isolate **7b** by flash chromatography on silica gel were complicated by partial spirocyclization reactions. However, this reactivity was advantageous for the stereodivergent synthesis of **6d** (Scheme 4); the treatment of crude **7b** with silica gel[15] in a one-pot operation afforded the spiro compound **11** as a 7:1 mixture of diastereomers. The relative configuration of the major diastereomer of **11**, as depicted in Scheme 4, was determined by comparing the characterization data to that of a previously reported derivative (see the Supporting Information for details). The crude diastereomeric mixture of **11** was treated with DBU in



Scheme 4. Stereodivergent synthesis of 3-aza-tricyclo[7.2.1.0^{1,6}]dodecane compounds. Bn = benzyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

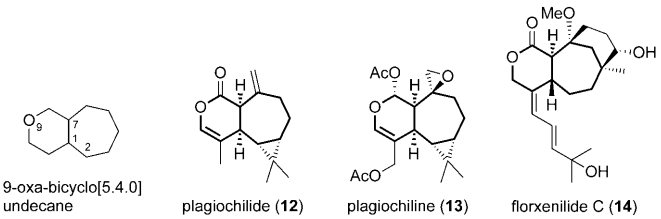
methanol to produce the diastereomer aldol products **6c**–**6e**. An analytical sample of the major diastereomer **6e**, crystallized from the 1:7 mixture of **6d**/**6e**, was then analyzed by X-ray diffraction to obtain the structure.[13] The d.r. of the products tends to indicate that retro-Michael processes did not occur under the conditions of the reaction,[16] which importantly allowed the synthesis of products **6d** and **6e** with an inverted relative configuration at C6 when compared to **6c**, thus paving the way to a concise and stereodivergent approach to compounds of type **6** in the aza series.

Finally, we explored the possibility of in situ retro-Dieckmann fragmentation of the tricyclo[7.2.1.0^{1,6}]dodecane **6a** to afford the 9-oxa-bicyclo[5.4.0]undecane ring system; a framework found for example in the insect antifeedant 2,3-secoaromadendrane sesquiterpenes plagiochilide (**12**) and plagiochiline (**13**),[17] or the rearranged xenicane diterpene florxenilide C **14**.[18] For this purpose, we used our previously developed conditions for the domino Michael–aldol–retro-Dieckmann sequence (MARDi cascade).[19] Thus, the treatment of compound **7a** with DBU in methanol, followed by aqueous acidic workup, afforded directly the cycloheptenes **15a** and **15b** as a 7:1 mixture of diastereomers (62% yield), with the major isomer exhibiting a *cis*-fused δ-lactone. The formation of **15** is believed to result from a six-step process: first, the domino Michael–aldol sequence from **7a** afforded **6a** in a comparable manner as described in Scheme 2. Then, and in contrast to the intermolecular version of the reaction,[19c] both diastereomers of **6a** underwent the expected domino retro-Dieckmann fragmentation with methanol, most probably with different kinetics, to afford two diastereomeric series of bicyclic cycloheptanols **16a** and **16b**. Under the basic reaction conditions, **16a** and **16b** are in dynamic equilibrium with their diastereomers **17a** and **17b**, both of which undergo a *trans*-lactonization,[20] followed by an irreversible elimination reaction to afford the monocyclic carboxylates **18a** and **18b**. Upon treatment with hydrochloric acid, the water-soluble δ-hydroxy carboxylates **18a** and **18b** undergo lactonization to produce the bicyclic δ-lactones **15a** and **15b**, respectively. Remarkably, compounds **15a** and **15b** (d.r. = 7:1) were obtained from the diazo compound **8a** in 45% yield overall, following two successive MBFTs, which involved four very simple components: diazo **8a**, homoallylic alcohol, acrolein, and methanol (Scheme 5).



Scheme 5. Synthesis of 9-oxa-bicyclo[5.4.0]undecane compounds.

In summary, expeditious stereoselective syntheses of terpene-like molecules have been accomplished by combinations of MBFTs, sometimes in a one-pot procedure, from very simple, abundant, and cheap starting materials. A rapid increase of natural-product-like complexity was achieved with good to excellent diastereoselectivities. The tricyclic compounds **6** were obtained from the diazo compounds **8** in one or two chemical operations involving the formation of



five chemical bonds (and two bonds breaking events) together with four new stereocenters, whereas the synthesis of **15** involved two reactions and more than ten bond-forming/breaking events. The avoidance of protecting-group chemistry and the strictly minimized number of purification processes undoubtedly contributed to the overall efficiency of the approach. The implementation of the methodologies presented herein, with the addition of more substituted and functionalized reaction partners, is expected to translate into a focused library of SMNP-like compounds, hopefully endowed with biological activities, and suitable for integration into medicinal chemistry and chemical biology research programs.

Experimental Section

See the Supporting Information for general experimental information, full experimental procedures, characterization data of all compounds, and NMR spectroscopy of all new compounds.

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Keywords: consecutive reactions · domino reactions · one-pot reactions · natural products · terpenoids

[1] a) G. M. Cragg, P. G. Grothaus, D. J. Newman, *Chem. Rev.* **2009**, *109*, 3012–3043; b) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461–477.

[2] a) R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2006**, *71*, 8329–8351; b) C. Cordier, D. Morton, S. Murrison, A. Nelson, C. O'Leary-Steele, *Nat. Prod. Rep.* **2008**, *25*, 719–737; c) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49; d) K. Kumar, H. Waldmann, *Angew. Chem.* **2009**, *121*, 3272–3290; *Angew. Chem. Int. Ed.* **2009**, *48*, 3224–3242.

[3] For efforts to clarify the terminologies of MBFTs, see: a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) *Domino Reactions in Organic Synthesis* (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, Weinheim, **2006**; d) Y. Coquerel, T. Boddaert, M. Presset, D. Mailhol, J. Rodriguez in *Ideas in Chemistry and Molecular Sciences: Advances in Synthetic Chemistry* (Ed.: B. Pignataro), Wiley-VCH, Weinheim, **2010**, Chapter 9, pp. 187–202.

[4] Recent reviews: a) K. C. Nicolaou, J. S. Chen, *Chem. Soc. Rev.* **2009**, *38*, 2993–3009; b) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439–4486; c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167–178.

[5] The following review articles include analyses of previous synthetic approaches to tricyclo[7.2.1.$0^{1,6}$]dodecane compounds: for **1** and related compounds, see : a) M. Presset, Y. Coquerel, J. Rodriguez, *Eur. J. Org. Chem.* **2010**, 2247–2260; for **2** and related compounds, see : b) J.-M. Gao, W.-J. Wu, J.-W. Zhang, Y. Konishi, *Nat. Prod. Rep.* **2007**, *24*, 1153–1189; for **3**–**5** and related compounds, see: c) H.-D. Sun, S.-X. Huang, Q.-B. Han, *Nat. Prod. Rep.* **2006**, *23*, 673–698.

[6] The numbering of atoms proposed in the structure of tricyclo[7.2.1.$0^{1,6}$]dodecane will be used throughout the manuscript.

[7] For previous preparation of analogues of **7** in two steps, see: T. Boddaert, Y. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2009**, *351*, 1744–1748; erratum: T. Boddaert, Y. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2009**, *351*, 2541.

[8] The reaction in CH_2Cl_2 was equally efficient, although slower than in toluene: M. Presset, Y. Coquerel, J. Rodriguez, *J. Org. Chem.* **2009**, *74*, 415–418.

[9] For reviews, see: a) Y. Coquerel, J. Rodriguez, *Eur. J. Org. Chem.* **2008**, 1125–1132; b) F. Nicks, Y. Borguet, S. Delfosse, D. Bicchielli, L. Delaude, X. Sauvage, A. Demonceau, *Aust. J. Chem.* **2009**, *62*, 184–207; for related CM reactions, see: c) A. Michaut, T. Boddaert, Y. Coquerel, J. Rodriguez, *Synthesis* **2007**, 2867–2871; d) T. Boddaert, Y. Coquerel, J. Rodriguez, *C. R. Chim.* **2009**, *12*, 872–875; for discussion, see: e) D. Dallinger, M. Irfan, A. Suljanovic, C. O. Kappe, *J. Org. Chem.* **2010**, *75*, 5278–5288.

[10] a) S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo, *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701; b) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu, W.-J. Xiao, *Angew. Chem.* **2008**, *120*, 2523–2526; *Angew. Chem. Int. Ed.* **2008**, *47*, 2489–2492; c) H. Fuwa, K. Noto, M. Sasaki, *Org. Lett.* **2010**, *12*, 1636–1639.

[11] a) M.-H. Filippini, R. Faure, J. Rodriguez, *J. Org. Chem.* **1995**, *60*, 6872–6882; b) M.-H. Filippini, J. Rodriguez, *Chem. Rev.* **1999**, *99*, 27–76.

[12] J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001–3003.

[13] CCDC-794646 (**6b·H_2O**), 794647 (**6c**) and 794648 (**6e**) contain the supplementary crystallographic data for thie paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] a) E. Vedrenne, H. Dupont, S. Oualef, L. Elkaïm, L. Grimaud, *Synlett* **2005**, 670–672. For a review on olefin metathesis reactions in the presence of a basic amine, see: b) P. Compain, *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.

[15] A. K. Banerjee, M. S. Laya Mimó, W. J. Vera Vegas, *Rus. Chem. Rev.* **2001**, *70*, 971–990.

[16] The aldolization may however be reversible under the reaction conditions.

[17] a) Y. Asakawa, M. Toyota, T. Takemoto, *Tetrahedron Lett.* **1978**, *19*, 1553–1556; b) Y. Asakawa, M. Toyota, T. Takemoto, I. Kubo, K. Nakanishi, *Phytochemistry* **1980**, *19*, 2147–2154.

[18] Y.-B. Cheng, J.-Y. Jang, A. T. Khalil, Y.-H. Kuo, Y.-C. Shen, *J. Nat. Prod.* **2006**, *69*, 675–678.

[19] a) Y. Coquerel, D. Bensa, V. Moret, J. Rodriguez, *Synlett* **2006**, 2751–2754 (erratum: Y. Coquerel, D. Bensa, V. Moret, J. Rodriguez, *Synlett* **2006**, 3368); b) Y. Coquerel, D. Bensa, A. Doutheau, J. Rodriguez, *Org. Lett.* **2006**, *8*, 4819–4822; c) Y. Coquerel, M.-H. Filippini, D. Bensa, J. Rodriguez, *Chem. Eur. J.* **2008**, *14*, 3078–3092; d) I. Reboul, T. Boddaert, Y. Coquerel, J. Rodriguez, *Eur. J. Org. Chem.* **2008**, 5379–5382.

[20] The *trans*-lactonization possibly proceeded through initial opening of the fused lactone with methanol, particularly in the case of **17b**.

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