DOI: 10.1002/ejoc.201101766

Organocuprate-Initiated Domino Michael–Intramolecular Aldol Reaction – Application to the Formation of Ring B of the Aglycon of Landomycins

Xavier Bugaut[a][‡] and Emmanuel Roulland*[a]

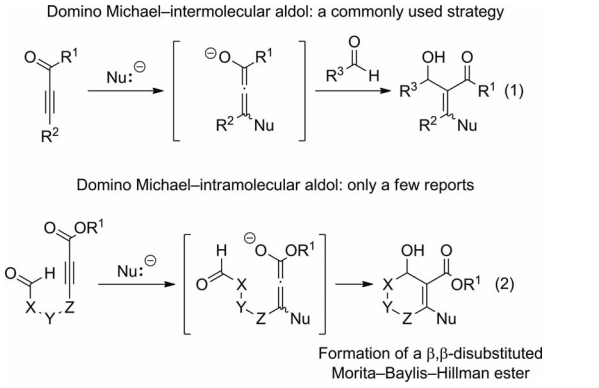
Keywords: Conjugate addition / Cyclization / Domino reactions / Landomycins / Cuprates

An innovative access to a β,β-disubstituted Morita–Baylis–Hillman motif, which is a potential intermediate en route to the synthesis of the aglycon of landomycins, is presented. It consists of a finely optimized organocuprate-initiated domino Michael–intramolecular aldol reaction. The use of TMSCl and DMAP as additives proved essential to ensure the success of this reaction sequence.

Introduction

The amine- or phosphane-catalyzed condensation of an acrylate with an aldehyde is a powerful catalytic transformation that enables access to the ubiquitous Morita–Baylis–Hillman ester motif.[1] However, an intrinsic limitation of this method is that it cannot afford β,β-disubstituted products. An alternative strategy to prepare them consists of the conjugate addition of a nucleophile to an electron-poor alkyne followed by the trapping of the intermediate allenolate by an aldehyde.[2,3] Even though the stepwise generation of the allenolate, followed by trapping with the aldehyde has been a widely used approach [Scheme 1, Equation (1)],[4] there are only a few reports on the intramolecular variant of this reaction, in which the Michael acceptor and the aldehyde are both present in the same reactant [Scheme 1, Equation (2)].[5–7]

Basically, this strategy requires conditions in which the highly reactive aldehyde function does not interfere with the first step of the process. Success has already been achieved with different *heteroatom-centered nucleophiles* such as lithium tellurophenolate,[5a] or iodide.[5c,5d] The synthetic usefulness of these transformations has been illustrated with an iodide-triggered key cyclization en route to the synthesis of kibdelone C, as recently reported by the group of Porco.[5d] To the best of our knowledge, there is only one example with a *carbon-centered nucleophile*: the group of Lu described the palladium-catalyzed enantioselective cyclization of *aryl*boronic acids and salicylaldehyde butynoate.[5b,8] We surmised that utilizing a di*alkyl*organocuprate in a comparable reaction would significantly increase the scope of this transformation.

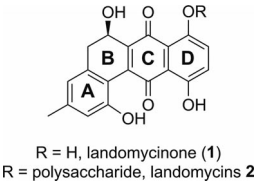


Scheme 1. Different strategies for the domino Michael–aldol reaction.

Herein, we wish to report how the aforementioned domino Michael–intramolecular aldol reaction has been used to efficiently construct ring B of landomycinone (**1**) (Figure 1). This fused tetracycle is the aglycon characterizing the members of the landomycin family **2**, which are natural products isolated from the fermentations of different strains of actinobacteria of the genus *Streptomyces*.[9] All these molecules exhibit interesting *in vitro* anticancer activity[10] and have therefore drawn the attention of several research groups, whose efforts could be divided into three main categories: genetic engineering approaches,[11] syntheses of the polysaccharides,[12] and synthetic studies of the aglycon.[13] Very recently, these efforts have culminated in the first total synthesis of landomycin A.[14] We contributed to this field by devising an original approach to an advanced intermediate to landomycinone (**1**), based on transition-metal-catalyzed cyclizations to create aromatic rings.[13c] However, this ini-

[a] CNRS, Institut de Chimie des Substances Naturelles (ICSN), UPR 2301,
Avenue de la Terrasse, 91198 Gif-sur-Yvette, France
Fax: +33-1-69077247
E-mail: emmanuel.roulland@icsn.cnrs-gif.fr
[‡] Present address: Aix-Marseille Université, iSm2, UMR CNRS 6263, Centre St Jérôme, service 541
13397 Marseille Cedex 20, France
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101766.

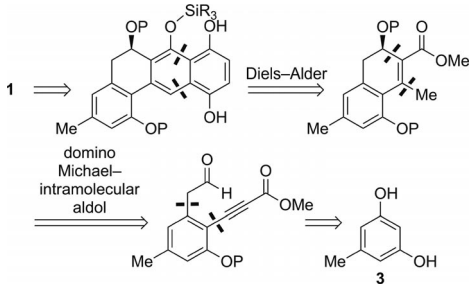
tial strategy was plagued with a long linear multistep sequence and with problems to reach the desired oxidation state at a late stage of the synthesis.



R = H, landomycinone (**1**)
R = polysaccharide, landomycins **2**

Figure 1. Landomycinone (**1**), the aglycon of landomycins **2**.

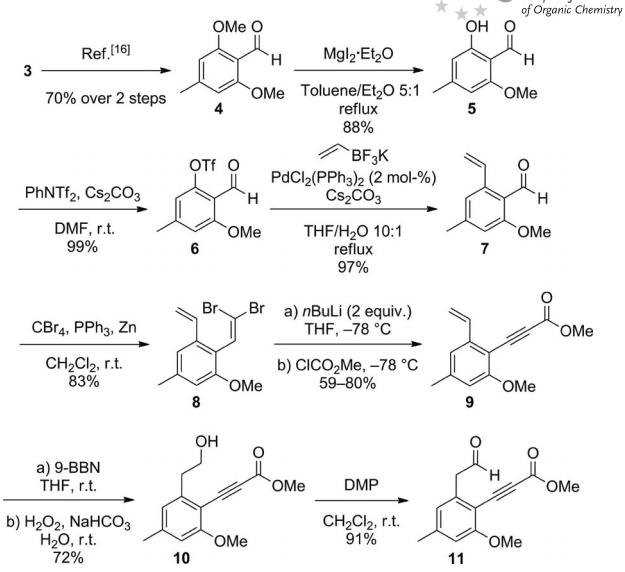
Our alternative retrosynthetic plan relies on the construction of the East part of the molecule by a Diels–Alder reaction with *p*-benzoquinone, similar to the one used by Kraus et al. for the synthesis of G-2N (Scheme 2).[15] The pivotal step would be the domino Michael–intramolecular aldol reaction to close ring B, starting from a bis-electrophile obtained from commercially available orcinol **3**.



Scheme 2. Retrosynthetic plan for the synthesis of landomycinone (**1**).

Results and Discussion

Dimethylation of orcinol **3** followed by *ortho*-lithiation and trapping of the resulting aryllithium with DMF afforded aldehyde **4** as described in the literature (Scheme 3).[16] Selective mono-demethylation with $MgI_2{\cdot}Et_2O$ in toluene heated to reflux gave phenol **5**,[17] which was quantitatively transformed into triflate **6**. A Suzuki–Miyaura cross-coupling with potassium vinyltrifluoroborate then afforded styrene **7** in excellent yield.[18] This first key intermediate served as starting point for the elaboration of bis-electrophile **11**. At first, the Michael acceptor was installed by using the Corey–Fuchs reaction. The modified procedure, with Zn, yielded the moderately stable dibromoolefin **8** more efficiently.[19] The second step afforded methyl propiolate **9**, even though the yield decreased as the reaction was scaled up. This phenomenon is explained by side reactions occurring on the styrene function. Afterwards, hydroboration with 9-BBN followed by oxidation with hydrogen peroxide yielded homobenzylic alcohol **10**, which was oxidized into the corresponding aldehyde **11** by using Dess–Martin periodinane.[20] In summary, this nine-step sequence with 19% overall yield delivered bis-electrophile **11**, with which the key domino Michael–intramolecular aldol reaction was optimized.

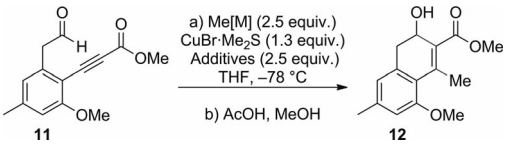


Scheme 3. Preparation of bis-electrophile **11** from orcinol **3**.

A thorough study of the addition conditions of dimethylcuprate to bis-electrophile **11** was conducted (Table 1). However, pathways concurrent to this domino Michael–intramolecular aldolization are possible, for example, direct addition of the organometallic species to the aldehyde function or even its enolization. A certain number of parameters needed to be adjusted to obtain a productive transformation: (1) utilizing $CuBr{\cdot}Me_2S$ as copper(I) source; (2) choosing THF as solvent; (3) proceeding by direct addition of the solution of bis-electrophile into the dimethylcuprate solution;[21] (4) using various additives. It is well-known that TMSCl accelerates 1,4-additions and causes them to be favored over 1,2-additions.[22] Moreover, this effect is further amplified when additives increasing the electrophilicity of the chlorosilane are concomitantly added.[23] With DMAP as second additive, cyclized product **12** was produced in encouraging yield (Table 1, Entry 1). Gratifyingly, in these conditions, neither the product of direct addition to the aldehyde nor that of Michael addition without cyclization could be detected.[24] HMPA and *N*-methylimidazole as additives gave lower yields than DMAP (Entries 2 and 3). We then tested the influence of the nature of the organometallic reagent, but organomagnesium proved less effective (Entry 4), whereas only starting material was recovered with organomanganese (Entry 5).[25] In addition, the use of a less nucleophilic methylcopper(I) (Entry 6) or a bulkier chlorosilane such as TBSCl (Entry 7) only resulted in complex mixtures. The results presented in entry 3 were encouraging, although they suffered from low reproducibility. At this stage, we hypothesized that these problems might result from the possible acid sensitivity of the product, which could aromatize by elimination of water.[26] Therefore, further improvements of the protocol were undertaken: quantities of the reagents were adjusted to avoid any trace of acid during the reaction (an excess of DMAP with respect to TMSCl was used) and the acidic quench (AcOH in MeOH) previously used to cleave the TMS group on the

alcohol was replaced by a basic one (K_2CO_3 in MeOH). All this allowed the isolation of key intermediate **12** with a reproducible 59% yield (Entry 8).

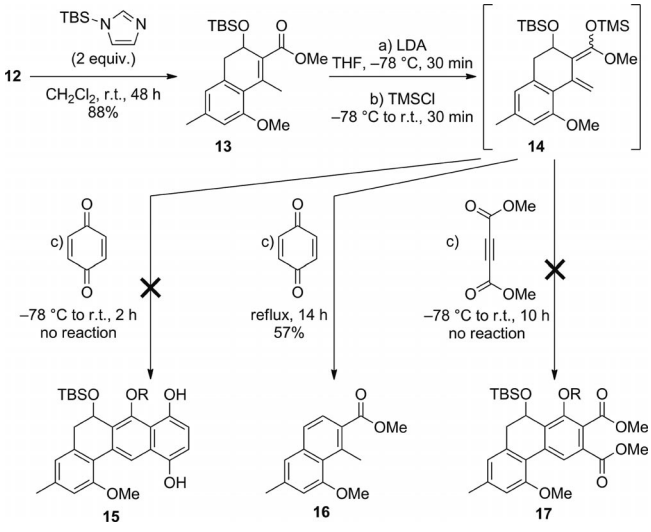
Table 1. Formation of ring B of landomycinone (**1**) by the domino Michael–intramolecular aldol reaction.[a]



Entry	Me[M]	Additives	Results
1	MeLi	TMSCl, DMAP[b]	**12** (47%)
2	MeLi	TMSCl, HMPA[c]	**12** (32%)
3	MeLi	TMSCl, NMI[d]	**12** (20%)
4	MeMgBr	TMSCl, DMAP	**12** (15%)
5	MeMnCl	TMSCl, DMAP	starting material[e]
6	MeLi[f]	TMSCl, DMAP	complex mixture
7	MeLi	TBSCl, HMPA	complex mixture
8[g]	MeLi	TMSCl, DMAP	**12** (59%)[h]

[a] Reactions were carried out in THF at –78 °C with dropwise addition of the solution of bis-electrophile into the dimethylcuprate solution. [b] 4-Dimethylaminopyridine. [c] Hexamethylphosphoramide. [d] *N*-Methylimidazole. [e] Even at room temperature. [f] Use of 1.3 equiv. of MeLi. [g] Quantities of the reagents were slightly modified: MeLi (4.0 equiv.), $CuBr·Me_2S$ (2.2 equiv.), TMSCl (2.0 equiv.), and DMAP (2.5 equiv.). The reaction was carried out at –50 °C. [h] AcOH was replaced by K_2CO_3 at the second stage.

The high acid sensitivity of alcohol **12** was confirmed when its protection as silyl ether was attempted. Classic conditions (TBSCl, imidazole or TBSOTf, 2,6-lutidine in CH_2Cl_2) gave disappointing results, as only low yields of desired product **13** were obtained and the formation of naphthalene derivative **16** (Scheme 4) was observed. Fortunately, a twofold excess of the neutral *tert*-butyldimethylsilylimidazole allowed a slow but clean and efficient protection.[27]



Scheme 4. Attempts to construct ring C of landomycinone (**1**) by a Diels–Alder reaction.

Having validated the strategy of the elaboration of ring B of landomycinone (**1**) by a fairly efficient domino Michael–intramolecular aldol process, we studied the possibility of setting up ring C by a Diels–Alder reaction (Scheme 4). Following the procedure described by Kraus et al. for the synthesis of G-2N,[15] the γ position of the α,β-unsaturated ester was deprotonated with LDA at –78 °C, and the resulting vinylogous enolate was trapped with TMSCl in order to obtain diene **14**. The formation of the latter could not be proved even when a bulkier silane was used, and adding HMPA during the deprotonation did not seem to have any influence on the process. Freshly sublimated *p*-benzoquinone was added, but no reaction occurred at room temperature and only starting material **13** was partly recovered after quenching. When the reaction mixture was heated to reflux, tetracyclic product **15** was not observed, and naphthalene **16** was isolated in 57% yield. The use of $B(OAc)_3$ as a mild Lewis acid to promote the cycloaddition also proved ineffective.[28] Alternatively, freshly distilled dimethyl acetylenedicarboxylate (DMAD) was tested as the dienophile, but once again no Diels–Alder product **17** was formed. We also tried to add DMAD directly after deprotonation, without trapping with TMSCl, to effect the same cyclization by a domino Michael–Claisen sequence, but this last attempt also failed.[29]

Conclusions

We have demonstrated that the domino Michael–intramolecular aldol sequence is a useful tool for the elaboration of the Morita–Baylis–Hillman ester motif. For this purpose, the conjugate addition of dimethylcuprate to a methyl propiolate followed by intramolecular trapping of the intermediate allenolate with an aldehyde allowed the efficient construction of ring B of landomycinone (**1**). TMSCl and DMAP were essential additives to ensure a selective process, in which no direct addition of the organometallic reagent to the aldehyde was observed. Further implementation of this innovative strategy to obtain the β,β-disubstituted Morita–Baylis–Hillman ester in the field of natural product synthesis, including the development of an asymmetric variant, is currently ongoing in our laboratory.

Experimental Section

Methyl 3-Hydroxy-8-methoxy-1,6-dimethyl-3,4-dihydro-naphthalene-2-carboxylate (12): MeLi (1.90 mL of a 1.6 M solution in Et_2O, 3.03 mmol, 4 equiv.) was added dropwise to a suspension of $CuBr·Me_2S$ (343 mg, 1.67 mmol, 2.2 equiv.) in THF (2 mL) at –50 °C. The reaction mixture was stirred for 2 h before slow addition of a solution of DMAP (232 mg, 1.90 mmol, 2.5 equiv.) in THF (3 mL) and TMSCl (192 μL, 1.52 mmol, 2 equiv.). A solution of aldehyde **11** (187 mg, 0.758 mmol, 1 equiv.) in THF (3 mL) was then added dropwise over 15 min, and the reaction mixture was stirred for 1 h at –50 °C. It was then quenched with 28% aqueous NH_3 (15 mL), stirred vigorously until the aqueous layer became blue, diluted with water (15 mL), and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water

(15 mL) and saturated aqueous $NaHCO_3$ (15 mL), dried with Na_2SO_4, filtered, and the solvents were removed under reduced pressure to yield a yellow oil. This oil was treated with K_2CO_3 (105 mg, 0.758 mmol, 1 equiv.) in MeOH (8 mL) for 15 min at room temperature to ensure complete cleavage of the TMS group on the secondary alcohol. The reaction mixture was then diluted with water (15 mL) and extracted with Et_2O (3 × 15 mL). Combined organic layers were washed with water (15 mL) and brine (15 mL), dried with Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (neutralized silica gel; heptane/EtOAc, 3:1 to 2:1) afforded Morita–Baylis–Hillman ester **12** (117 mg, 0.446 mmol, 59%) as a colorless amorphous solid.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the NMR spectra.

Acknowledgments

This work has been financially supported by the Institut de Chimie des Substances Naturelles (ICSN) and the Centre National pour la Recherche Scientifique (CNRS). Dr. Xavier Guinchard is acknowledged for his fruitful scientific advice and Charlotte Grosleron for her help in the preparation of the precursors.

[1] a) K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2815; b) A. B. Baylis, M. E. D. Hillman, Offenlegungsschrift 2155113, US Patent 3,743,669, **1972** [Chem. Abstr. **1972**, *77*, 34174q]; c) D. Basavaiah, G. Veeraraghavaiah, *Chem. Soc. Rev.* **2012**, *41*, 68–78.

[2] For an early general review on the domino Michael–aldol processes, see: R. J. K. Taylor, *Synthesis* **1985**, 364–392.

[3] For other nonrelated strategies that allow to access β,β-disubstituted Morita–Baylis–Hillman esters, see: a) G. Kanai, N. Miyaura, A. Suzuki, *Chem. Lett.* **1993**, *22*, 845–848; b) A. G. Schultz, Y.-J. Li, *Tetrahedron Lett.* **1997**, *38*, 2071–2072; c) J. Thibonnet, V. A. Vu, L. Bérillon, P. Knochel, *Tetrahedron* **2002**, *58*, 4787–4799; d) H. Menz, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 4795–4797; e) T.-K. Zhang, K. Yuan, X.-L. Hou, *J. Organomet. Chem.* **2007**, *692*, 1912–1919; f) K. Benda, W. Regenhardt, E. Schaumann, G. Adiwidjaja, *Eur. J. Org. Chem.* **2009**, 1016–1021.

[4] For selected examples, see: a) H.-X. Wei, S. Willis, G. Li, *Tetrahedron Lett.* **1998**, *39*, 8203–8206; b) H.-X. Wei, S. Willis, G. Li, *Synth. Commun.* **1999**, *29*, 2959–2966; c) T. Kataoka, H. Kinoshita, S. Kinoshita, T. Iwamura, S.-i. Watanabe, *Angew. Chem.* **2000**, *112*, 2448; *Angew. Chem. Int. Ed.* **2000**, *39*, 2358–2360; d) S. Kinoshita, H. Kinoshita, T. Iwamura, S.-i. Watanabe, T. Kataoka, *Chem. Eur. J.* **2003**, *9*, 1496–1502; e) S. V. Ley, A. Antonello, E. P. Balskus, D. T. Booth, S. B. Christensen, E. Cleator, H. Gold, K. Högenauer, U. Hünger, R. M. Myers, S. F. Oliver, O. Simic, M. D. Smith, H. Søhoel, A. J. A. Woolford, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12073–12078.

[5] a) J. P. Marino, H. N. Nguyen, *J. Org. Chem.* **2002**, *67*, 6291–6296; b) X. Han, X. Lu, *Org. Lett.* **2009**, *11*, 108–111; c) J. Ciesielski, D. P. Canterbury, A. J. Frontier, *Org. Lett.* **2009**, *11*, 4374–4377; d) D. L. Sloman, J. W. Bacon, J. A. Porco, *J. Am. Chem. Soc.* **2011**, *133*, 9952–9955.

[6] Ketones have also occasionally been used as second electrophiles: a) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Gränicher, J. B. Houze, J. Jänichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Mühlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, K. Tomooka, *J. Am. Chem. Soc.* **1997**, *119*, 2755–2756; b) J. Song, Q. Shen, F. Xu, X. Lu, *Org. Lett.* **2007**, *9*, 2947–2950; c) H. Wang, X. Han, X. Lu, *Tetrahedron* **2010**, *66*, 9129–9134.

[7] The aldehyde can also be part of the nucleophilic reactant: a) R. K. Gupta, M. V. George, *Tetrahedron* **1975**, *31*, 1263–1275; b) K.-J. Chang, D. K. Rayabarapu, C.-H. Cheng, *Org. Lett.* **2003**, *5*, 3963–3966; c) R. Shintani, K. Okamoto, T. Hayashi, *Chem. Lett.* **2005**, *34*, 1294–1295; d) T. Matsuda, M. Makino, M. Murakami, *Chem. Lett.* **2005**, *34*, 1416–1417; e) M. Yang, X. Zhang, X. Lu, *Org. Lett.* **2007**, *9*, 5131–5133.

[8] There are only a few related examples in the literature, using electron-poor alkenes as the first electrophile; with cyanide as nucleophile: a) E. Ciganek, *Synthesis* **1995**, 1311–1314; with organocuprates as nucleophiles: b) C. Schneider, O. Reese, *Chem. Eur. J.* **2002**, *8*, 2585–2594; c) D. B. England, J. Magolan, M. A. Kerr, *Org. Lett.* **2006**, *8*, 2209–2212; with arylboronic acids as nucleophiles and Rh catalysis: d) D. F. Cauble, J. D. Gipson, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111.

[9] a) T. Henkel, J. Rohr, J. M. Beale, L. Schwenen, *J. Antibiot.* **1990**, *43*, 492–503; b) S. Weber, C. Zolke, J. Rohr, J. M. Beale, *J. Org. Chem.* **1994**, *59*, 4211–4214; c) K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 127–195; d) L. Zhu, B. Ostash, U. Rix, M. Nur-e-Alam, A. Mayers, A. Luzhetskyy, C. Mendez, J. A. Salas, A. Bechthold, V. Fedorenko, J. Rohr, *J. Org. Chem.* **2005**, *70*, 631–638; e) recently, new family members that bear a slightly different aglycon have been reported: K. A. Shaaban, S. Srinivasan, R. Kumar, C. Damodaran, J. Rohr, *J. Nat. Prod.* **2011**, *74*, 2–11.

[10] a) R. T. Crow, B. Rosenbaum, R. Smith III, Y. Guo, K. S. Ramos, G. A. Sulikowski, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1663–1666; b) A. Korynevska, P. Heffeter, B. Matselyukh, L. Elbling, M. Micksche, R. Stoika, W. Berger, *Biochem. Pharmacol.* **2007**, *74*, 1713–1726; c) for a review on landomycins, see: B. Ostash, A. Korynevska, R. Stoika, V. Fedorenko, *Mini-Rev. Med. Chem.* **2009**, *9*, 1040–1051.

[11] For an overview of these studies, see ref.[10c]

[12] a) Y. Guo, G. A. Sulikowski, *J. Am. Chem. Soc.* **1998**, *120*, 1392–1397; b) W. R. Roush, C. E. Bennett, *J. Am. Chem. Soc.* **2000**, *122*, 6124–6125; c) B. Yu, P. Wang, *Org. Lett.* **2002**, *4*, 1919–1922; d) M. Zhou, G. A. O'Doherty, *Org. Lett.* **2008**, *10*, 2283–2286; e) H. Tanaka, S. Yamaguchi, A. Yoshizawa, M. Takagi, K. Shin-ya, T. Takahashi, *Chem. Asian J.* **2010**, *5*, 1407–1424.

[13] a) For an early biomimetic synthetic approach, see: K. Krohn, P. Frese, C. Freund, *Tetrahedron* **2000**, *56*, 1193–1196; b) for the first synthesis of landomycinone, see: W. R. Roush, R. J. Neitz, *J. Org. Chem.* **2004**, *69*, 4906–4912. c) Discrepancies between analytical data of "natural" and "synthetic" landomycinone induced Roush et al. to propose a revised structure for the aglycon. Nevertheless, further purification of the biosynthetic product solved this problem and confirmed structure **1**. See ref.[9d] and X. Bugaut, X. Guinchard, E. Roulland, *J. Org. Chem.* **2010**, *75*, 8190–8198.

[14] X. Yang, B. Fu, B. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 12433–12435.

[15] G. A. Kraus, G. Zhao, *J. Org. Chem.* **1996**, *61*, 2770–2773.

[16] a) B. M. Trost, H. C. Shen, L. Dong, J. P. Surivet, C. Sylvain, *J. Am. Chem. Soc.* **2004**, *126*, 11966–11983; b) M. Mondal, V. G. Puranik, N. P. Argade, *J. Org. Chem.* **2007**, *72*, 2068–2076.

[17] a) S. Yamaguchi, M. Nedachi, H. Yokoyama, Y. Hirai, *Tetrahedron Lett.* **1999**, *40*, 7363–7365; b) C. F. Nising, U. K. Ohnemüller, S. Bräse, *Angew. Chem.* **2006**, *118*, 313; *Angew. Chem. Int. Ed.* **2006**, *45*, 307–309.

[18] a) S. Darses, G. Michaud, J.-P. Genêt, *Eur. J. Org. Chem.* **1999**, 1875–1883; b) G. A. Molander, A. R. Brown, *J. Org. Chem.* **2006**, *71*, 9681–9686.

[19] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

[20] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.

[21] Reverse addition (of the solution of dimethylcuprate into one of the bis-electrophiles) afforded the desired product **12** in low yield along with the product of cyclization on which the methyl

group is absent. At first sight, the formation of the latter is rather surprising, as β-elimination from dimethylcuprate to afford copper hydride is impossible. However, related reductions have already been observed, especially when the concentration of dimethylcuprate is low, thereby modifying the aggregation of the organometallic species and altering its reactivity: a) B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, D. Parker, *J. Org. Chem.* **1984**, *49*, 3928–3938; b) J. Yang, D. F. Cauble, A. J. Berro, N. L. Bauld, M. J. Krische, *J. Org. Chem.* **2004**, *69*, 7979–7984.

[22] a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019–6022; b) A. Alexakis, J. Berlan, Y. Besace, *Tetrahedron Lett.* **1986**, *27*, 1047–1050; c) B. H. Lipshutz, S. H. Dimock, B. James, *J. Am. Chem. Soc.* **1993**, *115*, 9283–9284.

[23] a) A. R. Bassindale, T. Stout, *Tetrahedron Lett.* **1985**, *26*, 3403–3406; b) E. Nakamura, S. Matsuzawa, Y. Horiguchi, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4029–4032.

[24] Even though 1,4-addition is usually strongly favored over 1,2-addition when organocuprates are used, the high electrophilicity of aldehydes has already proved problematic in related processes; see refs.[8b–8d]

[25] a) G. Friour, G. Cahiez, J. F. Normant, *Synthesis* **1984**, 37–40; b) G. Cahiez, M. Alami, *Tetrahedron Lett.* **1989**, *30*, 3541–3544.

[26] Acid sensitivity is a chronic problem in the chemistry of landomycinone; see refs.[13b,13c,14]

[27] M. T. Reetz, G. Neumeier, *Liebigs Ann. Chem.* **1981**, 1234–1243.

[28] A. Guingant, M. M. Barreto, *Tetrahedron Lett.* **1987**, *28*, 3107–3110.

[29] R. S. Mali, P. G. Jagtap, *Tetrahedron Lett.* **1992**, *33*, 1655–1656.

Received: December 8, 2011
Published Online: January 4, 2012

