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Facile total synthesis of gymnoconjugatin A and B

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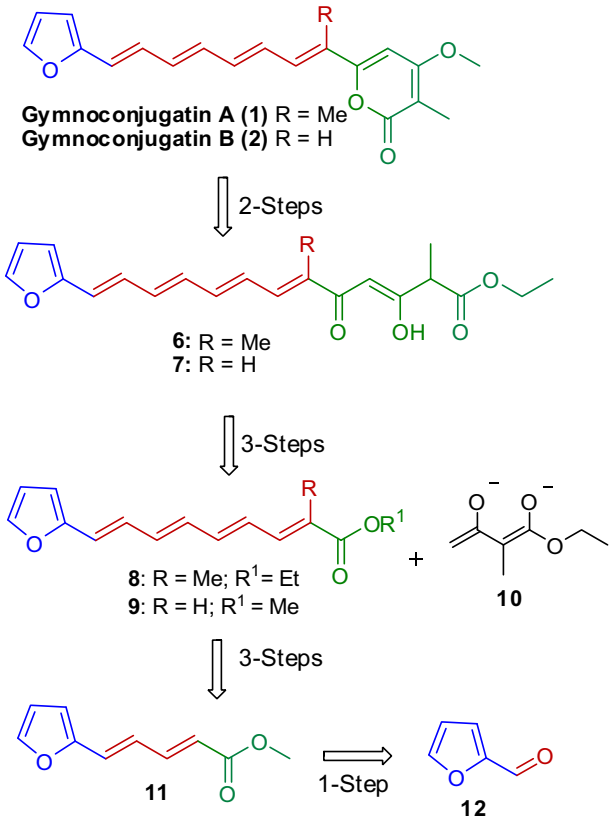
ABSTRACT

A facile total synthesis of the microbial natural products gymnoconjugatin A and B, isolated from soil microbe of *Gymnoascus reessii* has been accomplished using inexpensive raw materials, furfural and *trans*-methyl crotonate using Horner–Wadsworth–Emmons (HWE) and Wittig reactions.

Gymnoconjugatin A (**1**) and B (**2**) were isolated from the soil microbe of *Gymnoascus reessii* along with several known polyenyl-pyrroles including auxarconjugatin A (**3**) isorumbrin (**4**) (Fig. 1). The first total synthesis of **1** and **2** reported by Coleman and Walczak[1] was based on a linchpin coupling strategy using a boron/tin hetero-bis-metallated butadiene, Stille, and Suzuki–Miyaura couplings. Off late, Fang et al.[2] reported the synthesis of **3** and **4** using similar synthetic strategy. Despite sharing close structural homology, the biological studies carried out by the fore said groups have established the importance of 3-chloropyrrole moiety in eliciting biological activity. To gain further insights, it is essential to develop a robust synthetic route where-in different heterocyclic groups can be easily substituted in place of furan and pyrrole. Such a study may provide a molecular rationale for future therapeutic interventions in carcinogenesis.[1,2] We now report the stereocontrolled synthesis of **1** and **2** without using tin and palladium chemistry from fairly inexpensive starting materials.

The synthesis of gymnoconjugatin A and B was thought to retrosynthetically originate from the β-diketo ester **6** and **7** via base-mediated cyclization. It was proposed to construct the β-diketo ester by coupling dianion **10** with compounds **8** and **9** which in turn could be prepared from dienoate **11** in four steps from furfural (Scheme 1).

Our synthesis instigated with the conversion of methyl crotonate to the known phosphonate **13**[3] using Arbuzov reaction, while the conjugated phosphorus ylide **17**[4] was synthesized in three steps from methyl crotonate involving bromination, formation of



Scheme 1. Retrosynthetic analysis.

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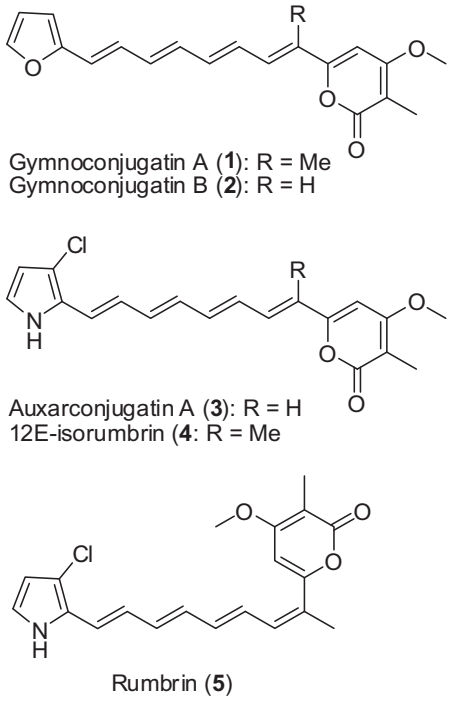
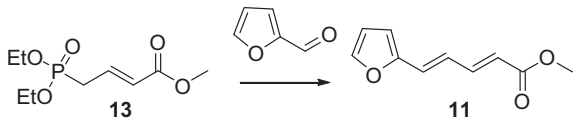


Figure 1. Structures of *Gymnoascus reessii* natural products.

Wittig salt and then ylide. The phosphorus ylide **16**[5] was derived from commercially available ethyl tiglate via allylic bromination followed by a Wittig reaction (Scheme 2).

The base-catalyzed Horner–Wadsworth–Emmons olefination of aldehydes and ketones with trialkyl phosphonocrotonates has been commonly used[6] for the preparation of 2,4-dienoates. A variety of bases including, NaH, *n*-BuLi, LDA, LiOH-4Å molecular sieves in THF, DBU[7] in CH_3CN have been frequently employed. However,

Table 1
Optimization of the HWE reaction conditions[a]

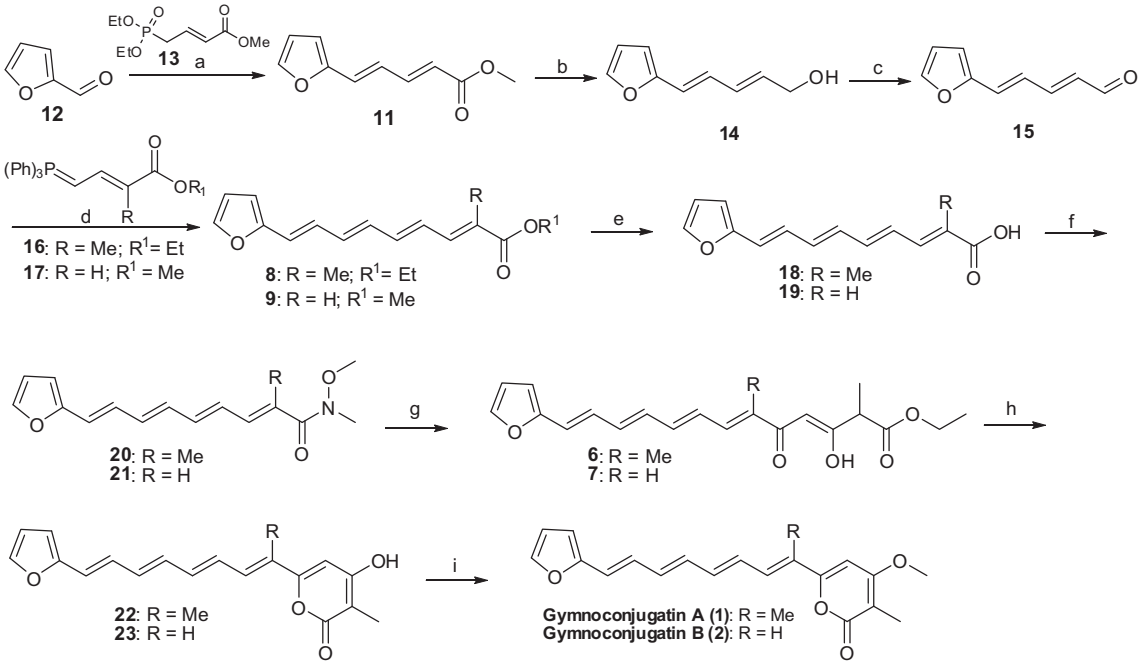


Entry	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	NaH	THF	0–rt	1	32
2	NaH	DMF	0–rt	1	81
3	NaH	DME	0–rt	1	18
4	LDA	THF	−78–40	1.5	30
5	*n*-BuLi	THF	−78–40	1.5	25
6	NaH	CH_3CN	0–rt	1	31
7	LiOH-MS	THF	Reflux	18	36
8	LiCl, DBU	CH_3CN	rt	5	26
9	K_2CO_3, DBU	CH_3CN	rt	5	28
10	*t*-BuOK	DMF	rt	3	21

[a] Reaction conditions: Furfural (1 equiv), Phosphonate **13** (1.2 equiv).
[b] Isolated yields of pure *trans*-dienoate **11**.

these conditions afforded the expected dienoate **11**[8] as a mixture of *cis* and *trans* isomers in poor yields. To overcome this problem, we examined a number of alternative conditions and found that sodium hydride in DMF condition worked exceptionally well with phosphonate **13**. Treatment of **13** with 1.5 equiv of sodium hydride in dry DMF under high dilution (20 volumes), followed by the addition of furfural afforded exclusively *trans*-dienoate **11** in 81% yield (Scheme 2; Table 1, entry 2). The geometry was confirmed by 1D-NOESY analysis and coupling constants.

Reduction of **11** with $LiAlH_4$ in diethyl ether furnished alcohol **14**[9], which was oxidized with Dess–Martin periodinane to provide aldehyde **15**.[10] Contrary to our expectation, aldehyde **15** when subjected to Horner–Wadsworth–Emmons (HWE) olefination with phosphonate **13** afforded the tetraene ester **9**[11] in low yields. However, decent yield was obtained by coupling **15** with stable



Scheme 2. Synthesis of gymnoconjugatin A and B. Reagents and conditions: (a) NaH, DMF, 0 °C–rt, 1 h, 81%; (b) $LiAlH_4$, diethyl ether, 5–10 °C–rt, 1 h, 95%; (c) Dess–Martin periodane, CH_2Cl_2, 0 °C–rt, 2 h, 82%; (d) compound **16** or **17**, MeOH, 0 °C–rt, 1 h, 48% (**8**), 54% (**9**); (e) LiOH, MeOH, THF, H_2O, rt, 5 h, 90% (**18**), 91% (**19**); (f) EDCI, HOBt, Et_3N, N(OMe) Me·HCl, CH_2Cl_2; 0 °C–rt, overnight, 62% (**20**), 65% (**21**); (g) sodium salt of ethyl 2-methylacetoacetate, *n*-BuLi, THF, −10–0 °C, 40 min, 58% (**6**), 60% (**7**); (h) DBU, toluene, reflux, 2 h, 70% (**22**), 68% (**23**); (i) Me_2SO_4, K_2CO_3, DMSO, rt, 2 h, 65% (**1**), 68% (**2**).

phosphorus ylide **17** in methanol at room temperature. The same sequence was applied for the synthesis of *trans*-tetraene ester **8** by reacting aldehyde **15** with phosphorus ylide **16** in 48% yield. The *trans*-tetraene esters (**8**, **9**) were hydrolyzed to *trans*-tetraene acids (**18**, **19**)[12] using lithium hydroxide in a mixture of THF, MeOH, and H_2O [4:1:1] in good yields.

The addition of dianion derived from β-keto esters to esters,[13] aldehydes[14], and imidazolyl amides[15] of simple substrates are well documented. Our analogous attempts on methyl ester **9** and its corresponding imidazolyl amide to obtain the β,δ-dioxocarboxylate **7** were not successful. However, conversion of corresponding acids (**18**, **19**) to the Weinreb amides[16] (**20**, **21**) followed by the addition of **10** in THF at −10 °C for 20 min, yielded compounds **6** and **7** in good yields. Cyclization of these β,δ-dioxocarboxylates was effected by heating with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)[17] to afford pyrones **22** and **23**. Methylation of hydroxyl groups was achieved using dimethyl sulfate[18] to afford gymnoconjugatin A (**1**) and B (**2**) (Scheme 2). The analytical data of synthetically accomplished gymnoconjugatin A and B were in agreement with the reported data.

In conclusion, we have developed an efficient protocol for the synthesis of gymnoconjugatin A and B. Unlike the earlier reported synthesis, where metal catalysts were used, the present route is economical. The present synthetic route developed with a view to support future structure–activity relationship studies for synthesizing other members of polyenyl-pyrrole and polyenylfurans series is currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.110.

References and notes

1. Coleman, R. S.; Walczak, M. C. *J. Org. Chem.* **2006**, *71*, 9841–9844.
2. Fang, Z.; Liao, P.-C.; Yang, Y.-L.; Yang, F.-L.; Chen, Y.-L.; Lam, Y.; Hua, K.-F.; Wu, S.-H. *J. Med. Chem.* **2010**, *53*, 7967–7978.
3. (a) Houllemare, D.; Outurquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1629–1632; (b) Baeckstrom, P.; Jacobsson, U.; Norin, T. *Tetrahedron* **1988**, *44*, 2541–2548.
4. (a) Kim, S.; Hatori, M.; Ojika, M.; Sakagami, Y. *Bioorg. Med. Chem.* **1998**, *6*, 1975–1982; (b) Mathieson, J. E.; Crawford, J. J.; Schmidtmann, M.; Marquez, R. *Org. Biomol. Chem.* **2009**, *7*, 2170–2175.
5. Lockwood, S. F.; U. S. Patent 20080221377.
6. (a) Wakasugi, K.; Nakamura, A.; Iida, A.; Nishii, Y.; Nakatani, N.; Fukushimac, S.; Tanabe, Y. *Tetrahedron* **2003**, *59*, 5337–5345; (b) Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem.* **1998**, *63*, 6757–6760.
7. (a) Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437–5440; (b) Ando, K.; Yamada, K. *Green Chem.* **2011**, *13*, 1143–1146; (c) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Su, G. *ARKIVOC* **2004**, *4*, 59–66.
8. Kato, T.; Suzuki, T.; Ototani, N.; Maeda, H.; Yarnada, K.; Kitahara, Y. *J. Chem. Soc., Perkin Trans. 1* **1977**, 206–208.
9. (a) Rallings, R. J.; Smith, J. C. *J. Chem. Soc.* **1953**, 618–622; (b) Yamano, Y.; Fujita, Y.; Mizuguchi, Y.; Nakagawa, K.; Okano, T.; Ito, M.; Wada, A. *Chem. Pharm. Bull.* **2007**, *55*, 1365–1370; (c) Novák, L.; Pirok, G.; Kovács, P.; Kolonits, P.; Szántay, Cs. *Tetrahedron* **1995**, *51*, 9367–9374.
10. (a) Bellassoued, M.; Salemkour, M. *Tetrahedron* **1996**, *52*, 4607–4624; (b) Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *119*, 1084–1088.
11. (a) Nagy, I.; Hajós, G.; Riedl, Z.; Egyed, O.; Pápai, I. *Tetrahedron* **2007**, *63*, 4730–4736; (b) Hanessian, S.; Botta, M. *Tetrahedron Lett.* **1987**, *28*, 1151–1154.
12. Mori, Y.; Asai, M.; Kawade, J.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315–5330.
13. (a) Yamaguchi, M.; Hasebe, K.; Uchida, M.; Irie, A.; Minami, T. *Tetrahedron Lett.* **1987**, *28*, 2017–2020; (b) Wolfgang, O.; Robert, M.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4713–4716; (c) Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Mathias, D. S.; Degen, S. J.; Golding, G. M.; Morgan, C. D.; Shih, R. A.; Mueller, K. A.; Scurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683–13696.
14. (a) Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901–2903; (b) Wolfgang, O.; Robert, M.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4713–4716.
15. Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uda, H. *J. Org. Chem.* **2002**, *67*, 5969–5976.
16. (a) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467–6470; For relevant Weinreb amide preparation: (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983 [for details, see Supplementary data].
17. (a) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748–8756.
18. (a) Fang, Z.; Liao, P.-C.; Yang, Y.-L.; Yang, F.-L.; Chen, Y.-L.; Lam, Y.; Hua, K.-F.; Wu, S.-H. *J. Med. Chem.* **2010**, *53*, 7967–7978; (b) Oikawa, H.; Suzuki, Y.; Katayama, K.; Naya, A.; Sakano, C.; Icihara, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 1225–1232.