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Catalytic Enantioselective Total Synthesis of (+)-Torrubiellone C

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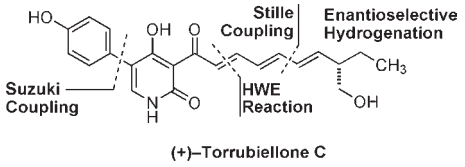
ABSTRACT



(+)–Torrubiellone C

Silyl-protected (*R*)-methyl 2-(hydroxymethyl)butanoate was obtained by an enantioselective Ir-catalyzed hydrogenation in high yield and selectivity. Elaboration of this building block via Takai and Stille reactions gave a protected hydroxy polyene chain, which was coupled to a 5-hydroxyphenyl-4-hydroxy-2-pyridone derivative by a modified Horner–Wadsworth–Emmons reaction. Deprotection gave synthetic (+)-torrubiellone C, which led to the assignment of the configuration of the natural product as (*R*).

Fungi that selectively infect and ultimately kill insects are physically controlling their insect hosts through a variety of interactions, some of which are postulated to be mediated by small molecules.[1] Among those, 5-phenyl-2-pyridone-polyenes[2] are found in several entomopathogenic fungi all over the world. The ecological function of these compounds remains unclear, which is surprising given their ubiquitous occurrence. Generic cytotoxicity or insecticidal activity appears, however, to be unlikely.[2] Therefore, one hypothesis includes that these compounds are involved in controlling the insect host by the producer.

In addition to these fascinating biological phenomena, the structural problem associated with these polyene pyridones, and in particular the configuration of the stereogenic center(s) in the side chain, often required the use of total synthesis for their ultimate assignment. We were intrigued by the question if the recently reported[3] torrubiellone C (**1**, isolated from spiders in Nam Nao National Park, Thailand) is of the same chirality (*homochiral* according to the original definition) compared to other members of this family such as **2**–**5**, originally isolated from different animals such as e.g. the mulberry small weevil, *Baris deplanata*, for compound **4**.[4] The homochirality of compounds found across fungi infesting various insect species could point to a common evolutionary ancestry of this class of compounds.

From a synthetic point of view, a structural feature of polypropionates is often represented by arrays of (skipped) methyl groups and many methods for their preparation have been developed.[5] Several members of the 5-phenyl-2-pyridone family display this pattern, which was addressed by our studies on the total synthesis of pyridone alkaloids.[6] In contrast, the hydroxymethyl group in torrubiellone C **1** leads to a different synthetic problem, i.e. the stereoselective preparation of a hydroxymethyl-ethyl

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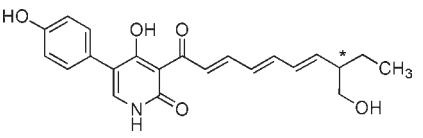
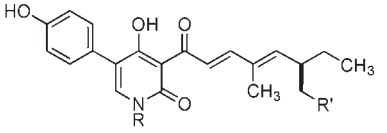
substituted stereogenic center.[7] Furthermore, only a few synthetic approaches to related structures such as pyridovericin **4** have been reported with low enantiomeric purity or low yields.[7c,8]



Torrubiellone C **1**



R = R' = H: Pretenellin B **2**
R = OH, R' = H: Tenellin **3**
R = H, R' = OH: Pyridovericin **4**
R = R' = OH: 15-Hydroxy Tenellin **5**

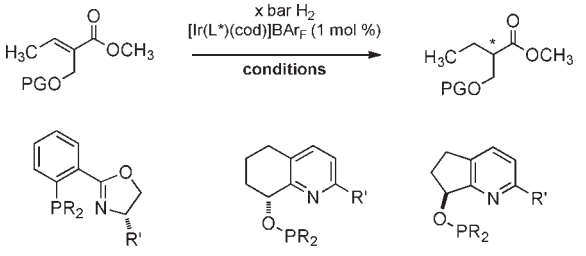
In addition, as pyridone alkaloids have recently been shown to be neuritogenic[6,9] and no biological activity had been assigned to torrubiellone C **1**,[3] we were intrigued to synthesize this compound for further biological assays. We wanted to avoid the use of enantiomerically pure starting materials, chiral auxiliaries, or enzymatic reactions as previously reported[7] and, therefore, planned to develop a catalytic enantioselective hydrogenation for the preparation of the enantiomerically enriched key building block (*R*)-methyl 2-(hydroxymethyl)butanoate.

The synthesis began with the preparation of a suitable precursor for enantioselective hydrogenation. We and others have previously demonstrated that α,β-unsaturated esters are valuable substrates for Ir-catalyzed enantioselective hydrogenations, allowing for the generation of the prerequisite stereogenic center.[5d,g,6] (*E*)-Methyl 2-(hydroxymethyl)but-2-enoate and the Si-protected derivatives as substrates for the hydrogenation could be prepared in multigram amounts (*E*/*Z* > 95:5) in four or five steps starting from methyl acrylate, following a previously published procedure (Table 1).[10]

A variety of conditions were evaluated to identify the optimal procedure (Table 1; for a more detailed analysis see Supporting Information (SI)). Unfortunately, the double bond in the unprotected hydroxyester could not be hydrogenated in the presence of Ir-catalysts even under forcing conditions (entry 1 and SI). Strikingly, control experiments with the Noyori Ru-BINAP catalyst also gave conversions below 1%. The introduction of a TBS-protecting group (entries 2−7) successfully tackled this general reactivity problem, and conversions usually above 99% could be achieved.

However, the screening of different chiral N,P-ligands with TBS-protected substrate did not result in the identification of a catalyst producing an enantiomeric purity above 82% ee (entry 7, analyzed by GC on chiral stationary phase after cleavage of the Si-protecting group; see also SI). Introduction of bulkier Si groups (entries 8−16) addressed this problem without losing the excellent conversion with a low catalyst loading. With the TBDPS-protected substrate and ligand **L3b**, very good enantioselectivity was observed (88% ee, entry 13), which could be increased to 90% ee by lowering the temperature (entry 16). Similar selectivity was observed with the TIPS-protected derivative (89% ee, entry 10).

Table 1. Identification of Optimal Conditions for the Catalytic Hydrogenation



entry	substrate PG =	ligand L	H_2 [bar]	temp [°C]	conversion[a] [%]	ee[a,b] [%] (configuration)
1	H		100	25	0	
2	TBS	**L1a**	50	25	>99	81 (*R*)
3	TBS	**L1b**	50	25	>99	74 (*R*)
4	TBS	**L1c**	50	25	>99	62 (*R*)
5	TBS	**L1d**	50	25	>99	79 (*R*)
6	TBS	**L2a**	50	25	>99	59 (*S*)
7	TBS	**L3b**	50	25	>99	82 (*R*)
8	TIPS	**L1a**	50	25	>99	72 (*R*)
9	TIPS	**L2a**	50	25	>99	67 (*S*)
10	TIPS	**L3b**	50	0	>99	89 (*R*)
11	TBDPS	**L1a**	50	25	>99	57 (*R*)
12	TBDPS	**L2a**	50	25	>99	76 (*S*)
13	TBDPS	**L3b**	50	25	>99	88 (*R*)
14	TBDPS	**L3b**	75	25	>99	87 (*R*)
15	TBDPS	**L3b**	25	25	>99	86 (*R*)
16	TBDPS	**L3b**	50	0	>99	90 (*R*)

[a] Determined for the corresponding hydroxyester on a chiral GC column. [b] (*R*) corresponds to (+), (*S*) to (−).

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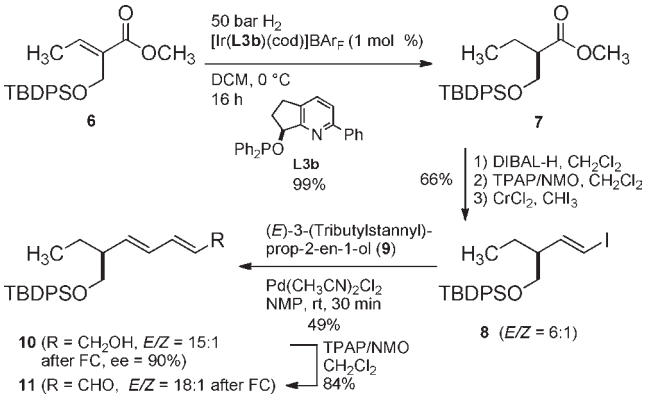
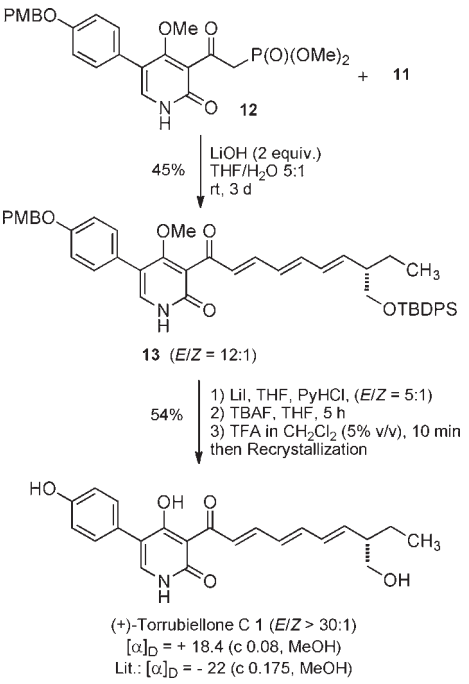
With optimal conditions identified, the hydrogenation was successfully reproduced several times on a 1 mmol scale of substrate **6** (1 mol % of Ir-catalyst, ligand **L3b**, 0 °C, 16 h, 50 bar of H_2 in CH_2Cl_2, 0.2 M), which resulted in sufficient material for the preparation of the side chain of torrubiellone C **1** (Scheme 1). After hydrogenation, ester **7** was reduced with DIBAL-H and oxidized with TPAP under careful control of the temperature to avoid racemization. The obtained aldehyde was subjected to a Takai olefination[11] yielding iodoolefin **8** as an inseparable mixture of *E*/*Z* isomers (*E*/*Z* = 6:1). Iodoolefin **8** was coupled with stannane **9**[12] to smoothly produce the homologated alcohol **10**. At this stage, the *E*/*Z* ratio could be increased to 15:1 by flash chromatography on silica gel. After oxidation and flash chromatography, the prerequisite aldehyde **11** for the envisaged Horner–Wadsworth–Emmons (HWE) reaction[13] was obtained in good yield and with an increased *E*/*Z* ratio (18:1).

Scheme 1. Preparation of the Side Chain **11**



HWE coupling of the unsaturated aldehyde to the known[6] functionalized pyridone phosphonate **12** was achieved in good yield following the previously described conditions (Scheme 2).[6] A mixture of THF/water and LiOH as a base were found to be essential to suppress side reactions. The reaction was conducted under exclusion of light in degassed solvents. Thus, protected torrubiellone C **13** was obtained in 45% yield and an *E*/*Z* ratio of >12:1 in favor of the desired all-*E* isomer. Cleavage of the methyl ether occurred in the presence of freshly crystallized LiI/pyridinium chloride in degassed THF at 60 °C.[6] These conditions were found to suppress the pronounced tendency of the side chain to isomerize. However, partial isomerization of one of the double bonds was observed. At this stage, no separation of the isomers was possible and the mixture was further deprotected with TBAF in THF. Again, no separation by flash chromatography or HPLC was feasible, and the mixture was finally treated with 5% TFA in CH_2Cl_2 for 10 min, yielding torrubiellone C **1** as a mixture of *E*/*Z* isomers. The isomerically pure synthetic natural product was finally obtained by recrystallization from MeOH/CH_2Cl_2/pentane (1:4:16) in a combined yield of 54% over the last three steps. The analytical data of the synthetic material were found to be identical in all respects in comparison with the published values,[3] except for the inverted $[\alpha]_D$ value. The configuration of naturally occurring (−)-torrubiellone C **1** is therefore assigned as (*R*). As a consequence, the hydroxylated natural product **1** is homochiral to, e.g., pretenellin B **2** or farinosone A.[6]

Scheme 2. Synthesis of (+)-Torrubiellone C **1**



In conclusion, the synthetic approach described yielded the enantiomeric natural product (+)-torrubiellone C **1** in 24 steps (13 step longest linear sequence). Salient features of this modular synthesis are the Ir-catalyzed enantioselective hydrogenation for the efficient preparation of (*R*)-methyl 2-(hydroxymethyl)butanoate as well as the modified HWE reaction to introduce a polyene moiety directly to a highly functionalized pyridone core structure without racemization. The neuritogenic properties of torrubiellone C as well as an enantioselective total synthesis of related pyridovericin **4** are currently under investigation.

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Supporting Information Available. Experimental procedures, full spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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