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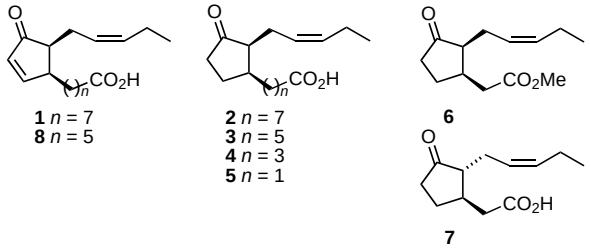
A New Synthesis Route to Enantiomerically Pure Jasmonoids**

Martin Ernst and Günter Helmchen*

Dedicated to Professor Volker Jäger on the occasion of his 60th birthday

12-Oxophytodienoic acid (12-OPDA) (**1**), ubiquitous in the plant kingdom, is the biosynthetic precursor for the jasmonoids **2**–**7**. These compounds result from **1** via the so-called octadecanoid cascade and participate as signaling compounds in a variety of processes.[1] 12-OPDA (**1**) itself originates from



1 $n = 7$
8 $n = 5$

2 $n = 7$
3 $n = 5$
4 $n = 3$
5 $n = 1$

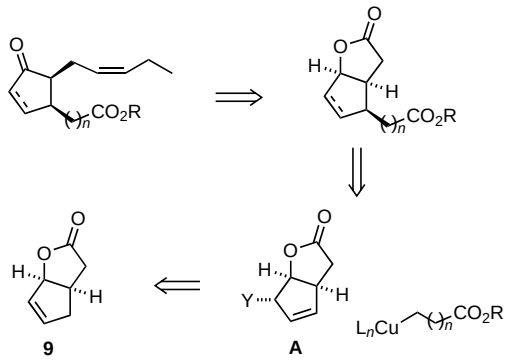
6

7

linolenic acid by oxidative cyclization. In 1997, dinor-oxophytodienoic acid (**8**), a hexadecanoid compound that is derived from hexadecatrienoic acid, was discovered and was shown to also possess pronounced biological activity.[2]

All of the jasmonoids possess an epimerizable *cis*-disubstituted cyclopentenone or cyclopentanone system. Many EPC syntheses exist for methyl epijasmonate (**6**) which is of great economical importance due to its use in fragrances.[3] For the other octadecanoids, a broadly applicable, diastereoselective route to the racemic compounds has been worked out by Crombie and Mistry.[4] The only asymmetric synthesis of enantiomerically pure **1**, presented by Grieco and Abood, employs an enzyme-catalyzed kinetic resolution.[5,15] We here report the development of an enantioselective synthetic route that could be applied to all of the jasmonoids, **1**–**8**, on the basis of a catalytic enantioselective process.

The concept of the synthesis is presented in Scheme 1 in the form of a retrosynthetic analysis. The key compound is an enantiomerically pure building block of general formula **A**



Scheme 1. General synthesis strategy for jasmonoids.

with a leaving group Y in allylic position. Herein, we could draw on studies by Roberts, Newton et al. who used the corresponding bromide, **A** with Y = Br, in the synthesis of prostaglandins, that is cyclopentanoids with *trans* configuration of the side chains.[6] They obtained the bromide by radical bromination of an isomer of lactone **9**. We wanted to introduce the carboxyalkyl side chain *cis* to the lactone function of the jasmonoids by an S_N2'-*anti*-reaction of intermediate **A** with an appropriate cuprate. Compound **A** was planned to be prepared from lactone **9** which was previously obtained in low selectivity by Pd-catalyzed asymmetric allylic alkylation of cyclopentenyl chloride using second-generation chiral phosphanyloxazoline ligands.[7]

With a third-generation phosphanyloxazoline, the ligand **L**,[8] we now obtained an enantiomeric excess of 95 % *ee* and a yield of 93 % in the allylic substitution with sodium dimethylmalonate (Scheme 2). The alkylated malonate was converted into the crystalline iodolactone whose enantiomeric purity was increased by recrystallization to > 99.9 % *ee*.[7] Dehydrohalogenation furnished the allylic lactone **9** in 70 % yield from **10**.

Bromolactone **11a** was prepared by radical bromination of **9** in CCl_4 under reflux in 60 % yield. In contrast to the racemate,[9] enantiomerically pure **11a** is an oil, and its purification by column chromatography laborious. Therefore, the series of allyl derivatives **14**–**17** was additionally prepared (Scheme 3). To access the non-natural enantiomers of the jasmonoids, *ent*-**9** was stereoselectively dihydroxylated,[10] and the resulting diol **12** was transformed into the allylic alcohol,[11] which was acylated. Both **12** and **13** as well as

[*] Prof. Dr. G. Helmchen, M. Ernst
Organisch-Chemisches Institut der Universität Heidelberg
Im Neuenheimer Feld 271, 69120 Heidelberg
Fax: (+49) 06221 544205
E-mail: g.helmchen@urz.uni-heidelberg.de

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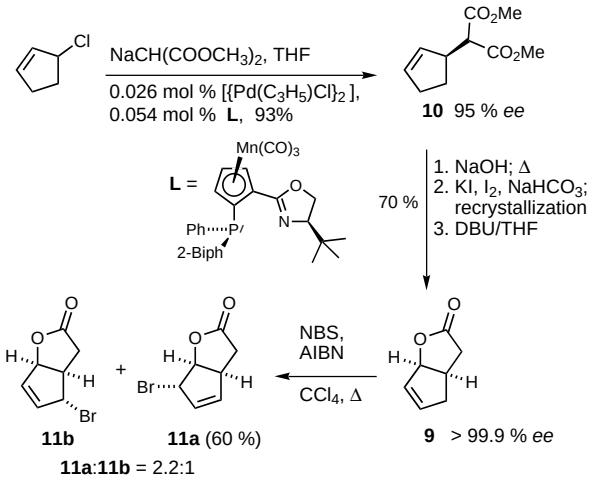
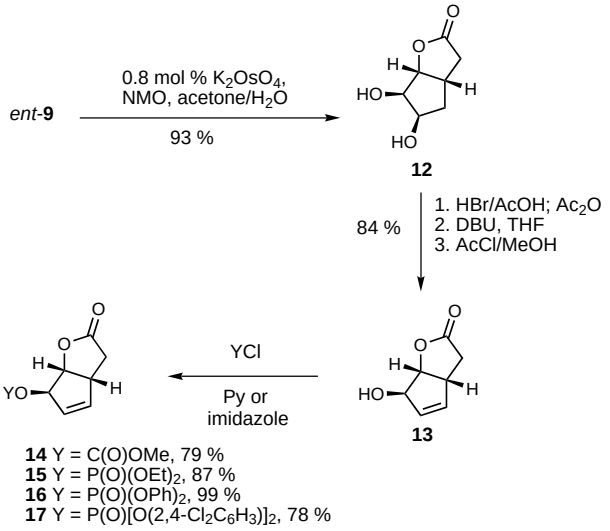
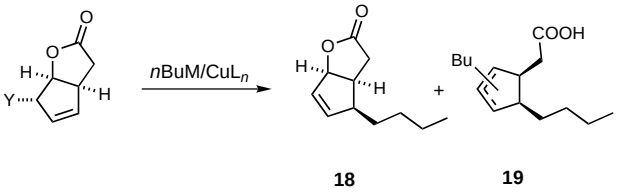


Scheme 2. Preparation of the bromolactone **11a**. Compound **11b** can be converted into a mixture of **11a** and **11b** by heating in toluene. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile, Biph = biphenylyl.



Scheme 3. Preparation of allylic substrates with different leaving groups. NMO = 4-methylmorpholine-*N*-oxide, Py = pyridine.

Table 1. Reactions of allylic substrates with *n*-butylcopper compounds.

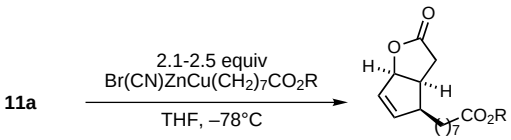


Substrate	Reagent	Equiv	**18** [%]	**19** [%]
11a	*n*BuLi/Li(2-thienyl)Cu(CN)	1.0	96	–
11a	*n*BuMgCl/CuBr·SMe$_2$	1.8	24	64
11a	*n*BuZnI/Li$_2$Cl$_2$Cu(CN)	13	quant.	–
11a	*n*BuLi/ZnCl$_2$/Li(2-thienyl)Cu(CN)	4.7	95	–
16	*n*BuLi/ZnCl$_2$/Li$_2$Cl$_2$Cu(CN)	2.5	95[a]	–
17	*n*BuLi/ZnCl$_2$/Li$_2$Cl$_2$Cu(CN)	2.7	85[a]	–

[a] In these cases *ent*-**18** resulted as the product.

The optimized reaction conditions were also applied to substrates **14**–**17** (Table 1). Only the phosphates reacted with zinc cyanocuprates, the electron-poor **17** displaying the highest reactivity, while **16** gave the highest yield. With diethylphosphate **15**, conversion was not complete even at prolonged reaction times.

Ester groups are tolerated in the preparation of organozinc compounds by reaction of halogen compounds with activated zinc in polar solvents.[13] Thus, the carboxyalkyl side chain needed for 12-OPDA (**1**) could be derived from methyl ω-bromooctanoate as well as *tert*-butyl ω-bromooctanoate (Scheme 4). The corresponding zinc cyanocuprates furnished yields of up to 97 % in the reaction with **11a**. Phosphate **16** was transformed into the enantiomeric product *ent*-**20** in 89 % yield.



Scheme 4. Introduction of the C_8 side chain by using a zinc cyanocuprate.

phosphate **16**, which proved to be particularly well suited for further transformations, are crystalline and, thus, the preparation of oxygenated allyl derivatives should be amenable to scale-up.

The S_N2'-*anti* reaction of **11a** with various organocopper reagents was investigated by using the introduction of a *n*-butyl substituent as model system (Table 1).[6] Use of exactly one equivalent of the organocopper compound afforded the monosubstitution product **18** in high yield. With an excess of monoorganocopper reagents or cyanocuprates, a domino reaction occurred, even at low temperature, in which allylic lactone **18** was opened, and a mixture of disubstituted carboxylic acids **19** was formed. Less reactive zinc cyanocuprates ("Knochel cuprates")[12] selectively displaced only bromide, even when used in high excess. Dependence on the type of organometallic precursor or the cuprate employed for transmetalation was not observed.

Lactone **20** was reduced with DIBAL-H to give the lactol which was transformed into the olefin in a *Z*-selective Wittig reaction (Scheme 5). The *Z*/*E* selectivity was in the range of 10:1. After separation of the isomers by flash chromatography, using silica gel impregnated with $AgNO_3$ as adsorbent, the pure *tert*-butyl ester was obtained in 55–76 % yield. Saponification of the *tert*-butyl ester and oxidation of the free acid with PDC afforded crude **1** in 50 % yield and pure **1** in 30 % yield after purification by MPLC. The methyl ester **26** was obtained in 71 % yield by oxidation of **25**. In analogy to **26**, the methyl esters of OPC-8:0 (**2**) and dinor-OPDA (**8**) were prepared, from **11a**, for the first time by enantioselective syntheses. In addition, *ent*-12-OPDA methyl ester was prepared from **16**.

The biological activity of the methyl esters of the various enantiomerically pure synthetic jasmonoids and their corresponding reduced precursors was assessed in the *bryonia*

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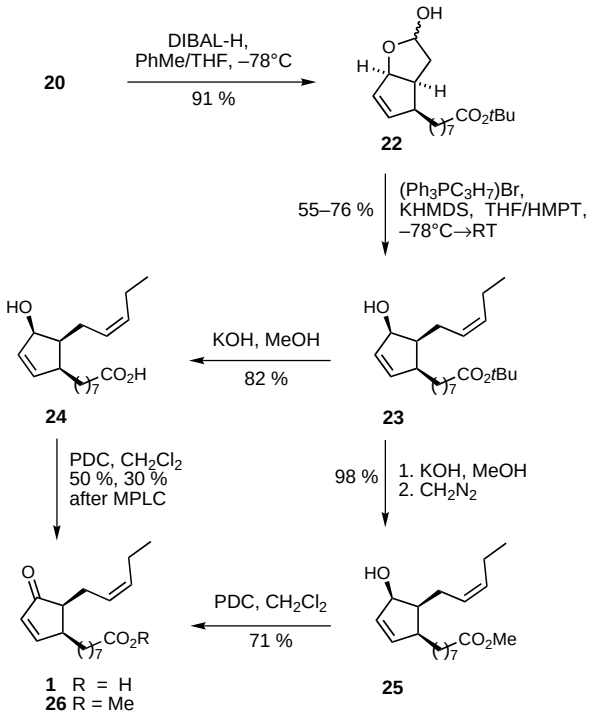

Scheme 5. Synthesis of 12-OPDA (**1**) and 12-OPDA methyl ester (**26**). DIBAL-H = diisobutylaluminum hydride, KHMDS = potassium hexamethyldisilazanide, HMPT = hexamethylphosphoric acid triamide, PDC = pyridinium dichromate.

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Palladium-Catalyzed Coupling of Alkyl Chlorides and Grignard Reagents**

Anja C. Frisch, Nadim Shaikh, Alexander Zapf, and Matthias Beller*

Organometallic cross-coupling reactions have proven extremely important in recent years for the synthesis of organic building blocks, and pharmaceutical and agrochemical derivatives. A topic of current interest in this area is the catalytic activation and subsequent functionalization reactions of C–Cl bonds not only for laboratory-scale synthesis but also for industrial applications.[1] To date the main focus has been the refinement of aryl and vinyl chlorides. Important contributions have been made, for example, in the area of Heck, Suzuki, and amination reactions of aryl chlorides.[2–8]

While catalytic nucleophilic substitution of $C(sp^2)$–Cl bonds is nowadays well established, the palladium-catalyzed refinement of alkyl chlorides has been largely neglected so far. The difficulty of catalytic nucleophilic substitution at $C(sp^3)$–Cl has been attributed to the ease of β-hydride elimination reactions of the corresponding alkylpalladium complexes. Nevertheless, Suzuki et al.[9] and Knochel et al.[10] demonstrated the possibility of palladium- and nickel-catalyzed coupling of alkyl bromides and alkyl boranes as well as organozinc derivatives. Furthermore, we were also able to show that palladium-catalyzed carbonylations of in situ generated α-amidoalkyl bromides proceed in good yields to the corresponding amino acid derivatives.[11]

Fu et al.[12] recently described the first catalytic coupling reactions of alkyl chlorides through a palladium-catalyzed Suzuki reaction. Kambe et al.[13] developed the efficient

[*] Prof. Dr. M. Beller, Dipl.-Chem. A. C. Frisch, M. Sc. N. Shaikh, Dr. A. Zapf
Institut für Organische Katalyseforschung
an der Universität Rostock e.V. (IfOK)
Buchbinderstrasse 5–6, 18055 Rostock (Germany)
Fax: (+ 49) 381-466-9324
E-mail: matthias.beller@ifok.uni-rostock.de

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