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Tetrahedron Letters 47 (2006) 4325–4330
Tetrahedron Letters

A synthetic approach to enfumafungin

Nicolas Zorn and Robert Lett*

Unité Mixte CNRS-AVENTIS Pharma (UMR 26) 102, route de Noisy, 93235 Romainville, France

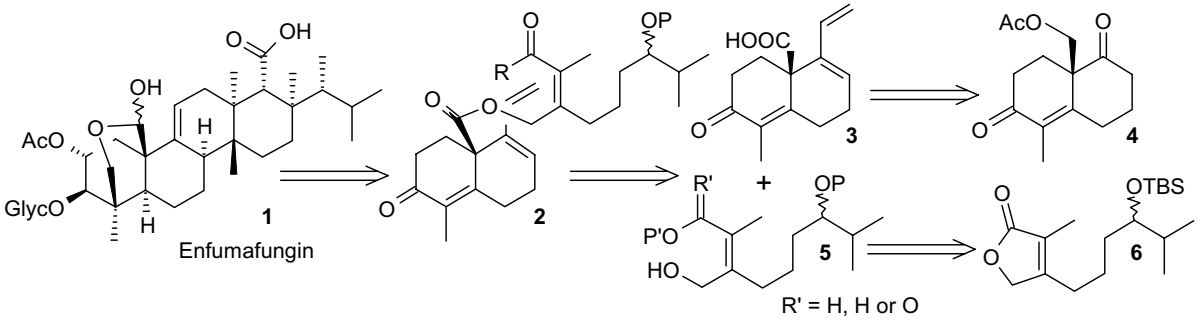
Received 8 March 2006; revised 19 April 2006; accepted 26 April 2006

Abstract—The stereospecific synthesis of the dienophile subunits **5** was achieved from the butenolide **6**. Ester **19** was obtained in 67% overall yield (2 steps), with no intermediate purification, by a sodium chlorite oxidation of the corresponding aldehyde in buffered conditions, followed immediately after extraction, by a Mitsunobu reaction of the relatively labile acid **3** with alcohol **13**. The synthesis of the α,β-unsaturated aldehydes **22** and **23** is also reported. Tentative IMDA reactions of **22** and **23** were examined in thermal conditions, or with a Lewis acid catalysis, and results are reported herein.

Lipopeptides are inhibitors of a novel target for antifungal drug development, the (1,3)-β-D-glucan synthase specific to the fungal cell wall synthesis,[1,2] and they appear to be very effective against serious invasive candidosis or aspergillosis for patients refractory to other previous drugs.[1] On screening natural compounds for novel structures having a mode of action comparable to that of lipopeptides, but having a potential for higher levels of oral bioavailability, enfumafungin **1** is a triterpene glycoside which was recently discovered at Merck[3] and shown to be a new lead as an inhibitor of (1,3)-β-D-glucan synthase.[4] Quite remarkably, its structure is completely different from those of other previous inhibitors.[2] Despite its interesting potential, no other synthetic effort toward enfumafungin has been reported to date. Our synthetic approach to enfumafungin **1** is based on an intramolecular Diels–Alder reaction (IMDA) of the ester **2** (Scheme 1).[5] The latter might be prepared from the optically active acid **3**, which was synthesized from (*S*)-(+)-**4** (ee = 85%),[6] and the dienophile subunit **5** which might be an α,β-unsaturated aldehyde or ester.[5] We herein report the stereospecific synthesis of the tetrasubstituted olefin **5**, via the disubstituted butenolide **6**, and also the preparation of some IMDA precursors like **2**.

1. Synthesis of the butenolide 6 (Scheme 2)

Tetronic acid **8** was obtained from **7** (62% overall yield) according to previous reports.[7] Conditions described by Grigg[8] with Tf_2O/DIPEA afforded triflate **9**, but in lower and less reproducible yields than reaction with



Scheme 1.

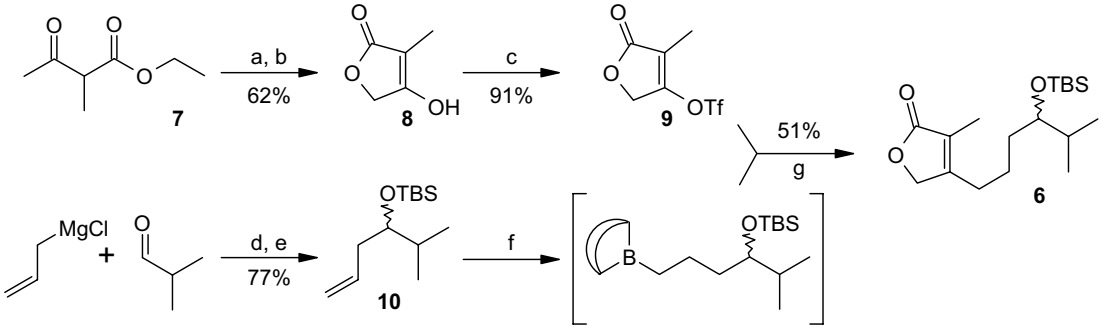
* Corresponding author at present address: ICMMO, UMR CNRS 8182, bâtiment 410, Université de Paris-Sud, 91405 Orsay Cedex, France. Tel.: +33 1 69 15 63 03; fax: +33 1 69 15 46 79; e-mail: robert.lett@icmo.u-psud.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.113

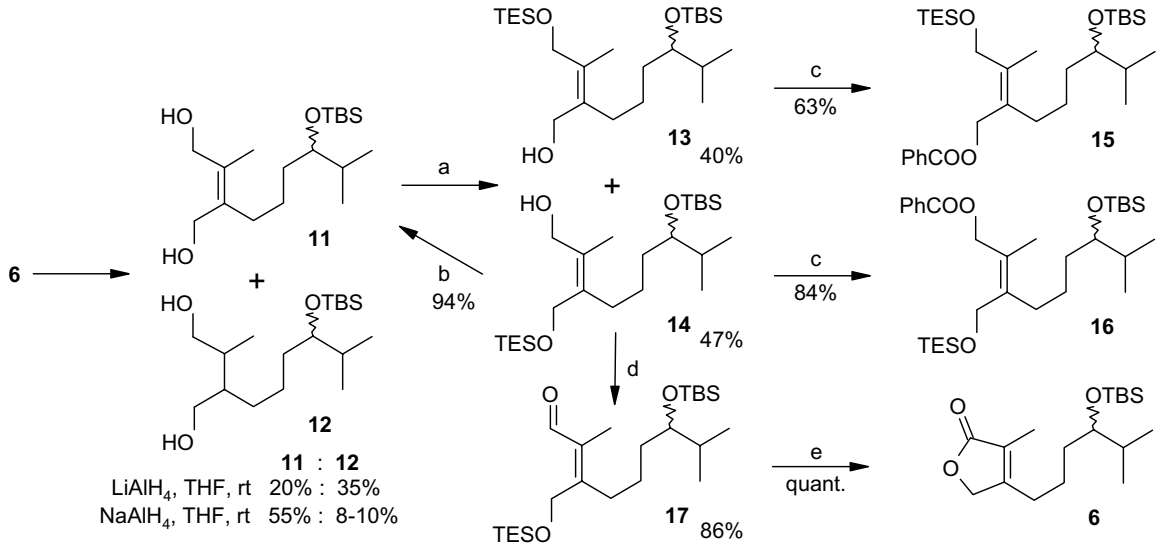
$PhNTf_2$/DIPEA which gave **9** in 91% yield after flash chromatography. The terminal olefin **10**, required for a B-alkyl Suzuki coupling[9] with **9**, was prepared in 78% yield over 2 steps, racemic since oxidation of the secondary alcohol into a ketone was planned further in the synthesis.[5] Complete conversion of the terminal olefin into the 9-alkyl BBN derivative appeared to be difficult with 1.05 equiv. BBN (0.5 M in THF, 0–40 °C). Use of excess 9-BBN gave side products after coupling and work-up. However, hydroboration of **10** in stoichiometric conditions and further one-pot Suzuki coupling afforded **6** in reproducible yields (48–51%), with 12–13% reisolated olefin **10**.

2. Synthesis of the dienophile subunit (Scheme 3)

In contrast with some examples of butenolides, monoalkyl[10] or dialkyl[11] substituted on the double bond, which were opened previously, all attempts to convert **6** (or 2,3-dimethylbutenolide as a model) into the corresponding methyl (or ethyl) ester—or to isolate the carboxylate salt—just led to degradation products in basic conditions at rt.[5] No reaction occurred in neutral transesterification conditions with $Ti(OiPr)_4$ in MeOH or EtOH,[12] from rt to 60 °C. Some deprotection of the TBS ether of **6** was only observed with $BF_3{\cdot}Et_2O$ (4 equiv, MeOH, rt). With 2,3-dimethylbutenolide as a model, buffered conditions with LiOH and 30% H_2O_2 in excess, at rt, led first to epoxidation of the double bond and only afterwards to the cleavage of the γ-lactone.[5] Thus, the 2,3-dialkyl substituted double bond appears to completely disfavor the opening of the γ-lactone, as was found earlier for dimethylmaleic anhydride where the monoester cannot be isolated either with a free carboxylic acid or a carboxylate anion.[13] On the other hand, the dimethyl ester can be obtained in good yield from dimethylmaleic anhydride.[14]



Scheme 2. Reagents and conditions: (a) Br_2 (1.05 equiv), $CHCl_3$, 0 °C to rt, 2 h; (b) crude bromination products mixture, neat, 130 °C, 2 h; (c) DIPEA (1.3 equiv), $PhNTf_2$ (1.25 equiv), CH_2Cl_2, 0 °C, 30 min; (d) allyl magnesium bromide (1 M in Et_2O, 1.1 equiv), Et_2O, 0 °C to rt, 1 h, 80%; (e) TBSCl (2 equiv), NMI (4 equiv), DMF, rt, 5 h, 97%; (f) addition of **10** (3 M in THF), at 0 °C, to 9-BBN 0.6 M in THF (1.05 equiv), then 0 °C to rt, 5 h; (g) $Pd(OAc)_2$ (10 mol %), K_3PO_4 (3 equiv), dioxane, then **9** (1.1 equiv), rt, 10 min, followed by addition of the crude 9-alkyl BBN solution in THF and subsequently 60 °C for 7 h.



Scheme 3. Reagents and conditions: (a) *n*BuLi (2.5 M in hexanes, 1 equiv) added to **6** (0.4 M) in THF, at −30 °C, 5 min, then rt for 5 min, and subsequently cooled to −20 °C, addition of TESCl neat (0.98 equiv), 20 min, followed by dilution with ether, NEt_3 quench and pH 7 buffer; (b) preformed solution of commercial $(HF)_n{\cdot}Py$/pyridine/THF (1:4:10) added to **14** (0.1 M) in THF, rt, 1 h; (c) DMAP (0.7 equiv), NEt_3 (4 equiv), PhCOCl (2 equiv), CH_2Cl_2, rt, 30 min; (d) Dess–Martin periodinane (1.1 equiv), pyridine (5 equiv), CH_2Cl_2, rt, 30 min; (e) *t*BuOH/H_2O/2-methyl-2-butene (4:2:1), $NaH_2PO_4{\cdot}2H_2O$ (2.5 equiv), tech. 80% $NaClO_2$ (5 equiv), rt, 1 h 15 min, then pH 3 buffer.

Therefore, we decided to obtain diol **11** (Scheme 3), although we could not expect a selective hydroxyl protection. Quite unusually, $LiAlH_4$ reduction of butenolide **6**, in THF at rt, afforded the saturated diol **12** as the major product (35%) and **11** in only 20% yield. Hence, $NaAlH_4$ in THF, at rt, gave the desired diol **11** in 55% isolated yield, but also still 8–10% of **12**. At this point, formation of the mono TES ether of diol **11** was considered, in order to allow further selective cleavage in the presence of the secondary OTBS. Monosilylation could be achieved quite efficiently, but afforded the two monoprotected TES ethers **13** (40%) and **14** (47%) with almost no selectivity, 2% of the bis-TES ether and 5% recovered diol **11** after chromatography. The structures of alcohols **13** and **14** were established by 2D NMR (HSQC, HMBC) and selective NOE of benzoates **15** and **16**, derived respectively from each pure isomer. Structures of **13** and **14** were also unambiguously proven since the Dess–Martin[15] oxidation of the more polar isomer (10:90 EtOAc–heptane) gave aldehyde **17** (86%). This aldehyde was cleanly and quantitatively converted into the starting butenolide **6**, directly by a chlorite oxidation in buffered conditions.[16]

The unwanted isomer could be recycled efficiently: cleavage of the TES ether of **14** could be achieved very selectively with the (ca 70:30) HF·pyridine solution, buffered by pyridine in THF, at rt, to afford pure diol **11** in 94% yield (Scheme 3).

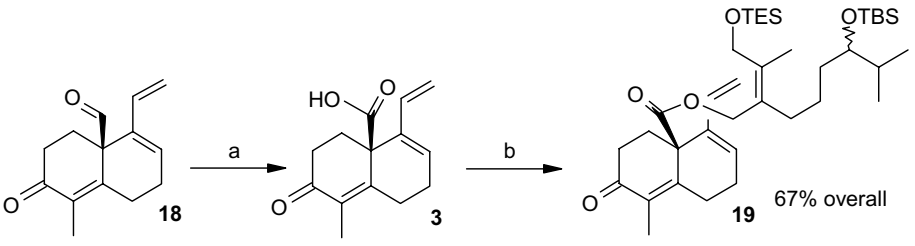
3. Formation of ester 19 (Scheme 4)

A sodium chlorite oxidation of aldehyde **18**,[5] in buffered conditions at rt,[16] afforded in a very clean reaction the carboxylic acid **3**, relatively labile even in dilute solutions at rt. Evaporation to dryness of solutions of **3** (under reduced pressure at rt) led to considerable degradation, and even concentrations higher than 0.05 M in EtOAc or CH_2Cl_2 had to be avoided.[5] Therefore, in addition to very mild conditions (usually at rt in non-polar solvents), a Mitsunobu reaction[17] appeared to us to have some advantages over a carboxylic acid activation: the carboxylate anion should be formed by protonation of the zwitterionic adduct produced by reaction of the phosphine with DEAD, carboxylate which might be expected to be more stable than the acid. Moreover, in some previous work in an other project,[18] a Mitsunobu reaction showed to be much more efficient than an acyl activation for obtaining the ester of a very highly hindered carboxylic acid, although the related pK_A of the carboxylic acid is known to be a very critical factor.[19] A major difficulty in our case was also to obtain a ca 0.01–0.02 M anhydrous solution of acid **3** in a non-polar solvent such as toluene for the Mitsunobu reaction, since the chlorite oxidation was usually achieved in *t*BuOH–H_2O and also because the extract could not be evaporated to dryness.[5] These problems could be solved by optimization of an extraction procedure involving successive replacement of solvents under reduced pressure (EtOAc to cyclohexane, and then toluene), always keeping the concentration of **3** below ca 0.01–0.02 M and maintaining temperature at rt. The nature of the solvents used allowed azeotropic removal of traces of water and the volumes were minimized in order to shorten the procedure with respect to the stability of the acid. The desired ester **19** was thus obtained in 67% overall yield from aldehyde **18** (Supplementary data). It is also worth to point out that adding DEAD to the stirred toluene solution of the mixture acid **3**/alcohol **13**/PPh_3 was found to give better results than the sequential addition of the acid and then alcohol solution, to the preformed phosphine–DEAD adduct.[5]

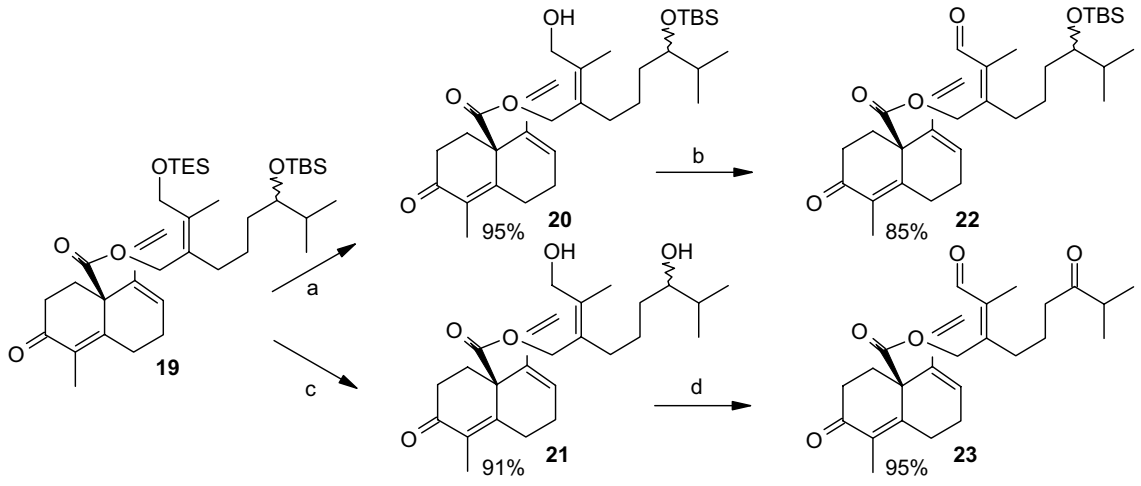
4. Preparation of IMDA precursors (Scheme 5)

Selective deprotection of the TES ether of **19** was reliably achieved very cleanly with the commercial $(HF)_n$·Py solution (ca 70:30, w:w), buffered by addition of anhydrous pyridine to get HF·$Py_{1.4}$, in THF at 0 °C. These conditions gave alcohol **20** in 95% yield, and no traces of diol **21** or other products were observed. On the other hand, diol **21** was best obtained (91% yield) by modifying the conditions and adding pyridine to get a $(HF)_3$·Py stoichiometry, in THF at rt. Noteworthy, the use of (ca 70:30) $(HF)_n$·Py solution, or BF_3·Et_2O in CH_2Cl_2 at rt, or TBAF 1M in THF (2.5 equiv) at rt, led mainly to by-products and degradation.[5]

Finally, a Dess–Martin oxidation in CH_2Cl_2 at rt, in the presence of pyridine, gave α,β-unsaturated aldehydes **22** (85%) and **23** (95%), after chromatography. The IMDA



Scheme 4. Reagents and conditions: (a) *t*BuOH/H_2O/2-methyl-2-butene (7:2:1), NaH_2PO_4·$2H_2O$ (2.5 equiv), tech. 80% $NaClO_2$ (5 equiv), rt, 65 min, then diluted by EtOAc, pH 3 buffer; EtOAc extract of the crude acid **3** concentrated to a ca 0.01–0.015 M solution, then addition of cyclohexane to get a mixture cyclohexane/EtOAc (ca 1:4, v:v), concentration to a ca 0.03 M solution under reduced pressure at rt, subsequent addition of an equal volume of toluene and reevaporation (under reduced pressure, rt) to get a final dry toluene solution ca 0.02 M of acid **3**; (b) preceding solution added to azeotropically dried alcohol **13** (1.2 equiv, 0.35 M) in anhyd toluene and PPh_3 (4 equiv), then dropwise DEAD addition (neat, 4 equiv), and subsequently 30 min at rt.



Scheme 5. Reagents and conditions: (a) commercial $(HF)_n$·Py/pyridine/THF (1:4:27, v:v:v), **19** (0.084 M), rt, 15 min; (b) Dess–Martin periodinane (2.5 equiv), pyridine (10 equiv), CH_2Cl_2, rt, 95 min; (c) commercial $(HF)_n$·Py/pyridine/THF (1:0.7:1.9, v:v:v), **19** (0.075 M), rt, 3 h 35 min; (d) Dess–Martin periodinane (4 equiv), pyridine (20 equiv), CH_2Cl_2, rt, 30 min.

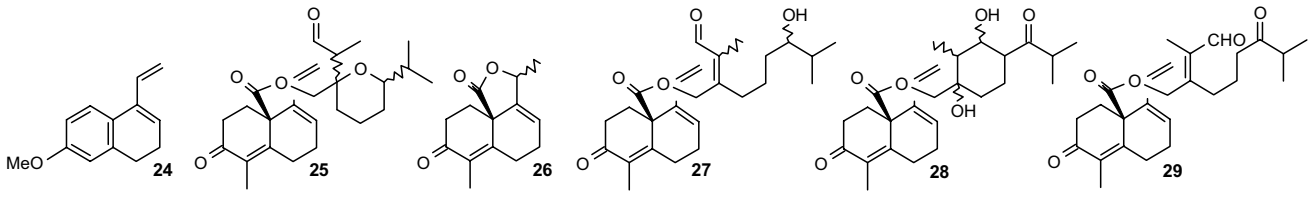
precursors **22** and **23** were thus obtained in, respectively, 54% and 58% overall yield from aldehyde **18** (4 steps).

5. First tentative IMDA reactions

The planned IMDA was initially one of the problems we considered as a challenge in our approach. We were aware of only two previous examples of Diels–Alder reactions which had involved an α,β-unsaturated ketone with a tetrasubstituted double bond.[20] Noteworthy, these IMDA were achieved under thermal conditions and, moreover, involved substituted cycloalkenones, already known to be quite unreactive and to usually require a Lewis acid catalysis or (and) high pressure.[21] Although butenolides are quite poor dienophiles in intermolecular reactions, very efficient IMDA were also achieved under thermal conditions with substituted butenolides, in pioneering achievements by Kametani[22] and Ikegami,[23] and extended later by several groups.

Considering the diene moiety, Dane's diene **24** or parent bicyclic dienes (lacking the 3-methoxy group or having a saturated A ring) were shown to react in intermolecular Diels–Alder reactions with substituted cyclopentenones in Lewis acid catalyzed conditions or (and) with high pressure.[21] Under pure thermal conditions, 3-methyl-3-cyclopentene-1,2-diones are required as dienophiles with **24** as shown by Quinkert estrone synthesis,[24] or dialkylmaleic anhydrides with 1-OTBS-1,3-butadiene as in the recent merrilactone A synthesis of Danishefsky.[25]

Therefore, the α,β-unsaturated aldehydes **22** and **23** were thought to be reasonable IMDA precursors to be initially investigated. Several reactions were first run under thermal conditions, using ca 5 mM solutions of **22** or **23** in anhydrous degassed solvents. In the presence of BHT, no reaction was observed by heating for several hours from 60 °C to 110 °C in toluene, or at temperatures lower than 160 °C in dodecane. At 160 °C, degradation occurred in about 4 h in dodecane or mesitylene, and much more rapidly without BHT, yielding products which could not be further characterized.



We then examined the reactions of either **22** or **23** in the presence of different Lewis acids, directly in an NMR tube under inert atmosphere, either in benzene-d_6 or in $CDCl_3$. Reactions were monitored by ^1H NMR at 400 MHz. Lewis acid excess (2–5 equiv) was added, at rt, due to the possible coordination to the different oxygenated sites, although the α,β-unsaturated aldehyde should be favored for the complexation in dynamic equilibria.[26] Reactions of **22** in benzene-d_6 with $SnCl_4$, or Et_2AlCl, led to degradation products which could not be purified and characterized. Reactions of **22** with either $BF_3{\cdot}Et_2O$ or $(C_6F_5)_3B$, in $CDCl_3$, gave after purification **25**, **26** and a mixture of *E* and *Z* α,β-unsaturated aldehydes **27**. It appeared that deprotection of the TBS ether resulted in the formation of the Michael adducts **25**. This led us to study the reactions of the parent keto-aldehyde **23**. Use of $TiCl_4$ or Et_2AlCl gave only intractable reactions. Reaction with $BF_3{\cdot}Et_2O$ in $CDCl_3$ at rt gave **26** (35%) and a mixture of diastereomers **28** (30%) corresponding to an intramolecular aldol reaction

occurring after 1,4-addition of water. Reaction of **23** with $(C_6F_5)_3B$ gave 40% of reisolated **23**, 30% of a mixture of **23** and **29**, and 25% of **28**. The use of higher temperatures in conjunction with milder Lewis acids gave no cycloadduct with **23** in various conditions. Degradation of **23** occurred at about 80–100 °C with $Sc(OTf)_3$, 125–140 °C with $Zn(OTf)_2$, and was slower at 100 °C with $Yb(OTf)_3$ than with $Sc(OTf)_3$.[5]

At this point, our results showed that the conjugated diene isomerization, which could be expected, was not a major problem here. The IMDA precursors showed to have a good thermal stability up to ca 160 °C, in the presence of BHT. On the other hand, in the presence of a Lewis acid, major problems appeared to be linked to 1,4-additions on the tetrasubstituted double bond of the dienophile. We presently could not achieve the IMDA of **22** or **23**.[5] Hence, further experiments would require either another type of catalysis, or other IMDA precursors.

Acknowledgements

We thank the staff of the Analytical Department of the Research Center at Romainville and also Hoechst Marion Roussel, Aventis Pharma and the CNRS for a Ph.D. Grant to N. Zorn, the Direction des Recherches Chimiques of HMR and Aventis Pharma for support of this work.

Supplementary data

Supplementary material associated with this article contains detailed experimental procedures for the preparation of acid **3** and ester **19**, and spectral data (IR, ^1H and ^{13}C NMR, MS) of the methyl ester of **3** and of **19**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.113.

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