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Structure Assignment of Lagunapyrone B by Fluorous Mixture Synthesis of Four Candidate Stereoisomers

Fanglong Yang, Jeffery J. Newsome, and Dennis P. Curran*

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received July 6, 2006; E-mail: curran@pitt.edu

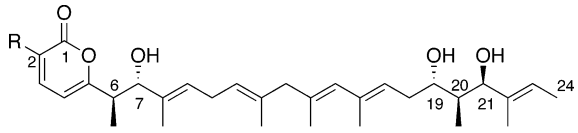
Abstract: Techniques of fluorous mixture synthesis have been used to make four candidate stereoisomers for the natural product lagunapyrone B. A quasiracemic mixture of vinyl iodides whose component configurations at C19−21 were encoded by fluorous silyl groups was fused to a central fragment by a Negishi coupling. A separate quasiracemic mixture of pyrone fragments whose component configurations at C6,7 were also encoded by fluorous silyl groups was synthesized and demixed. Stille coupling of the resulting pure quasienantiomers with the quasiracemic mixture provided two quasi-diastereomeric samples, which were demixed and detagged to provide all four lagunapyrone B stereoisomers. Lagunapyrone was assigned the 6*R*,7*S*,19*S*,20*S*,21*R* configuration by comparison of optical rotations.

Introduction

During an investigation of the secondary metabolites of estuarine actinomycetes, Fenical and co-workers reported the isolation and structure assignment of lagunapyrones A, B, and C (**1**−**3**, Figure 1).[1] These compounds constitute a novel skeletal class of natural products and feature a 24-carbon chain consisting of an α-pyrone ring with two adjacent stereocenters (C6,7) separated by 11 carbon atoms (four alkenes and three methylene groups) from a second group of three stereocenters (C19−21) terminating in another alkene. All seven of the double bonds in the backbone of the lagunapyrones are trisubstituted, and the three compounds differ in the nature of the group attached to C2: **1**, R = CH_3; **2**, R = C_3H_7; **3**, R = C_4H_9. Lagunapyrone B **2** exhibits moderate activity (ED_{50} = 3.5 μg/mL) against a human colon cancer cell line.

The two-dimensional structure (constitution) of the lagunapyrones was assigned primarily by analysis of 1D and 2D NMR spectra. Assignment of the relative configuration as anti at C-6 and C-7 was accomplished by comparison of vicinal proton coupling constants to calculated values and synthetic models. The relative configuration of C-19 through C-21 was assigned as anti,syn by converting lagunapyrone B **2** to an acetonide, which exhibited diagnostic chemical shifts in its ^{13}C NMR spectrum[2] and NOE effects in its ^1H NMR spectrum. However, the absolute configurations of the lagunapyrones could not be assigned, and neither could the configurations of the two remote groups of stereocenters be assigned relative to each other. Accordingly, there are still four possible structures for each of the natural products.

Despite the novel skeleton and interesting biological activity, there have not been any reports of synthetic efforts toward the lagunapyrones.[3] Recently developed techniques of fluorous mixture synthesis[4] have shown power in preparing small stereoisomer libraries (2−32 members) of several natural products.[5−7] We set out to simultaneously prepare all four candidate isomers for lagunapyrone B **2** by a fluorous mixture synthesis approach, and we report herein the successful attainment of this goal. By optical rotation comparison of the synthetic



lagunapyrones **1**, R = CH_3
2, R = $CH_2CH_2CH_3$
3, R = $CH_2CH_2CH_2CH_3$

6,7-*anti*-19,20-*anti*-20,21-*syn*
(6*R*,7*S*,19*S*,20*S*,21*R*)-isomer is shown,
also possible: (6*R*,7*S*,19*R*,20*R*,21*S*),
(6*S*,7*R*,19*S*,20*S*,21*R*), and (6*S*,7*R*,19*R*,20*R*,21*S*)

Figure 1. One of four possible stereostructures for lagunapyrones A−C (**1**−**3**).

(1) Lindell, T.; Jenson, P. R.; Fenical, W. *Tetrahedron Lett.* **1996**, *37*, 1327−1330.
(2) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9−17.
(3) Piericidins coexist with the lagunapyrones and have some structural resemblance. See: (a) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704−15705. (b) Keaton, K. A.; Phillips, A. *J. Am. Chem. Soc.* **2006**, *128*, 408−409.
(4) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769.
(5) Short review: Zhang, W. *Arkivoc* **2004**, 101−109.
(6) (a) Zhang, Q. S.; Lu, H. J.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36−37. (b) Dandapani, S.; Jeske, M.; Curran, D. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12008−12012. (c) Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 9447−9462. (d) Wilcox, C. S.; Gudipati, V.; Lu, H. J.; Turkyilmaz, S.; Curran, D. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 6938−6940. (e) Fukui, Y.; Brückner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, *8*, 301−304. (f) Curran, D. P.; Moura-Letts, G.; Pohlman, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2423−2426. (g) Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; Gudipati, V.; Wilcox, C. W. *J. Am. Chem. Soc.* **2006**, *128*, 9567−9573. (h) Curran, D. P.; Zhang, Q.; Lu, H.; Gudipati, V. *J. Am. Chem. Soc.* **2006**, *128*, 9943−9956.
(7) (a) Zhang, Q. S.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774−5781. (b) Zhang, Q. S.; Curran, D. P. *Chem.-Eur. J.* **2005**, *11*, 4866−4880.

10.1021/ja064812s CCC: $33.50

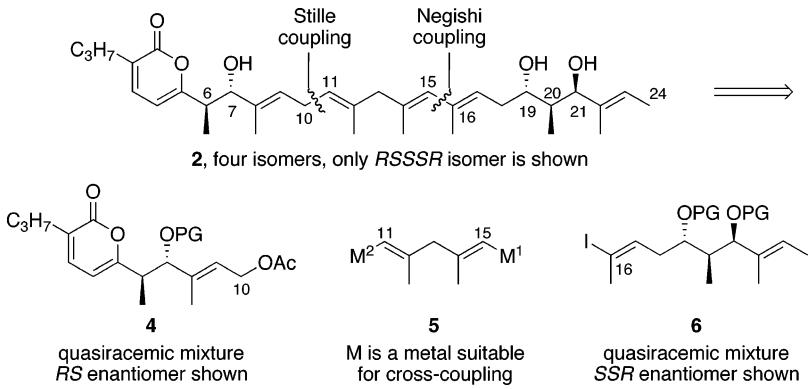


Figure 2. Retrosynthetic analysis of lagunapyrone B identifies three fragments.

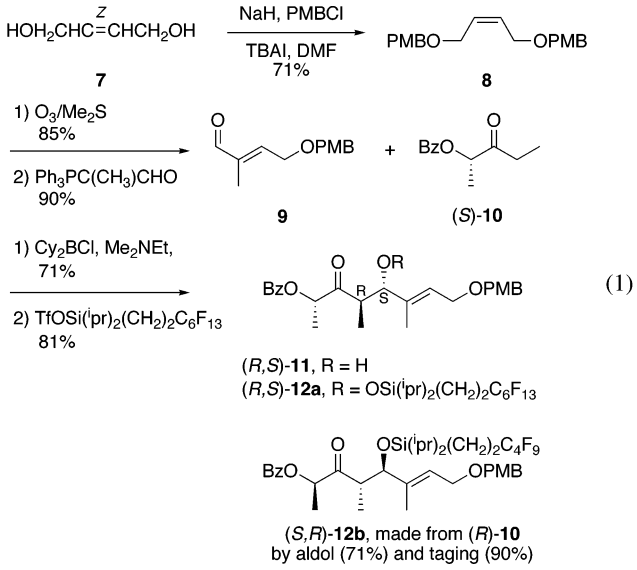
compounds to the natural sample, we assign the 6*R*,7*S*,19*S*,-20*S*,21*R* configuration to lagunapyrone B.

Results and Discussion

Figure 2 shows a partial retrosynthesis of lagunapyrone B **2**. We divided the molecule into left and right fragments, **4** and **6**, which we planned to make as quasiracemic mixtures[7] with configurations encoded by fluorous tags in the protecting groups (PG). These fragments would then be bridged together with symmetric middle fragment **5** by a Negishi coupling[8] to make the conjugated diene (C15,16) and a Stille coupling[9] to make the skipped diene (C10,11). This provides a mixture of four fluorous-tagged quasi-isomers ready for demixing and detagging to provide lagunapyrone and three isomers. This kind of double tagging strategy was recently validated in the synthesis of passifloricin.[6f] In practice, we deviated from the plan by using a middle fragment of lower symmetry than **5** to facilitate the couplings, and by demixing and detagging of one of the fragments (**4**) prior to the final coupling because of steric problems with that fragment.

The premix stage of the synthesis of α-pyrone fragment is summarized in eq 1. (*Z*)-2-Buten-1,4-diol **7** was converted to the bis-PMB ether **8** under standard conditions. Ozonolysis and Wittig reaction then provided aldehyde **9** as a single *E*-isomer. This aldehyde was then subjected to a Paterson *anti*-aldol reaction[10] with (*S*)-**10** to provide (*R*,*S*)-**11** as a single isomer in 71% isolated yield after flash chromatography. The hydroxy group of **11** was protected by silylation with in situ generated fluorous TIPS triflate[11] bearing the C_6F_{13} group to encode the 6*R*,7*S* configuration in (*R*,*S*)-**12a**. Likewise, reaction of **9** with (*R*)-**10** (not shown) and silylation with the fluorous TIPS triflate $TfOSi(^iPr)_2(CH_2)_2C_4F_9$ provided the quasienantiomer (*S*,*R*)-**12b** with the 6*S*,7*R* configuration encoded by the C_4F_9 group.

Quasienantiomers **12a** and **12b** were then mixed in a 1/1 ratio, and the synthesis was continued with quasiracemate M-**12a**,**b** as summarized in Scheme 1. (From here on, structures are drawn with configurations of the natural product lagunapyrone for simplicity; however, all compounds bearing the "M" prefix are fluorous-tagged mixtures of two quasienantiomers.) Standard cleavage of the α-benzoyloxyketone M-**12a,b** provided aldehyde M-**13a**,**b** in 90% overall yield.[12] This aldehyde was used without success as a precursor for a number of standard α-pyrone syntheses;[13,14] accordingly, we deployed a new α-pyrone synthesis to build this key group.

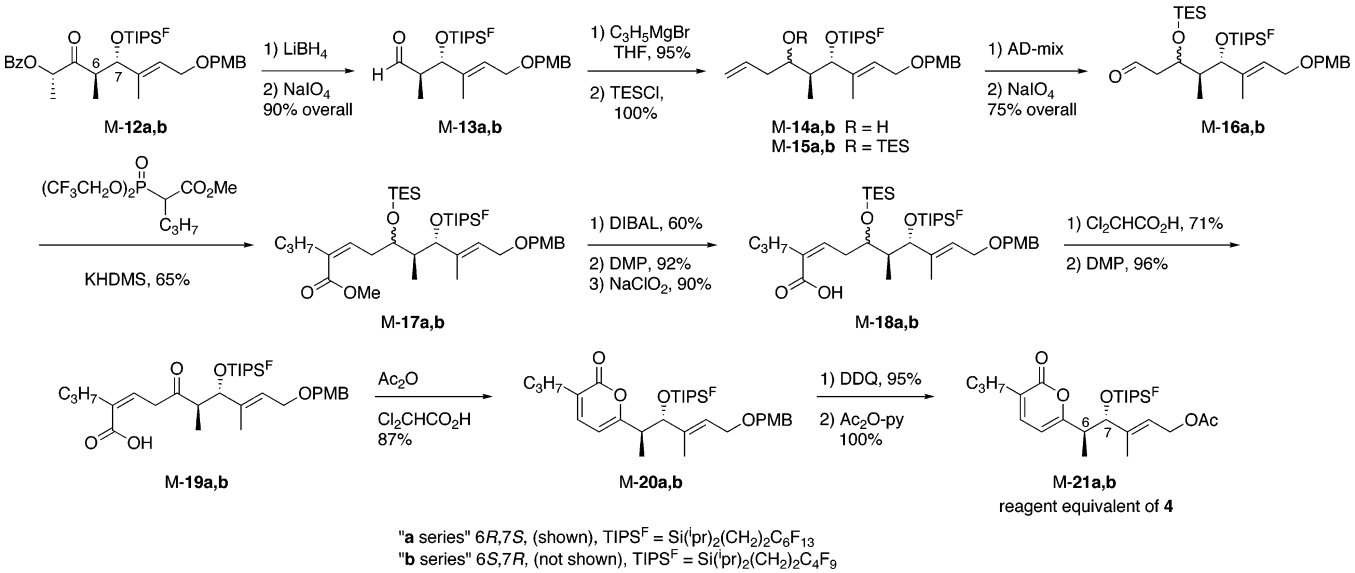


(1)

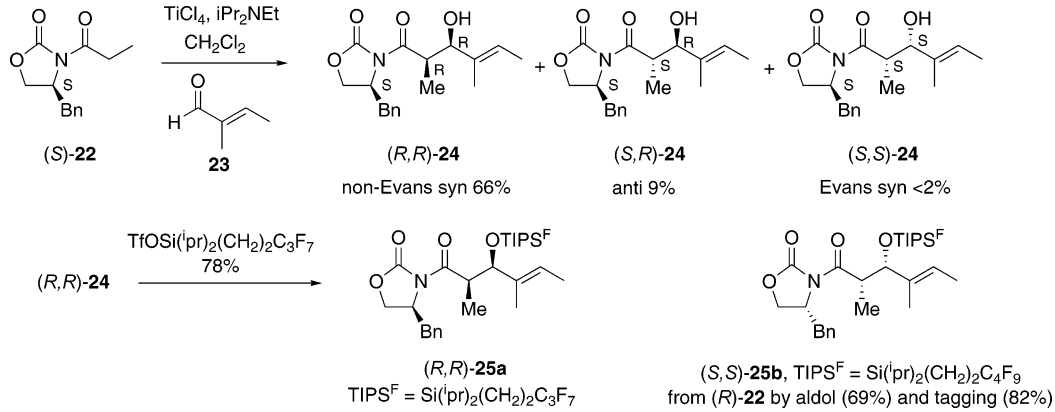
Addition of allylmagnesium bromide to M-**13a**,**b** provided a stereoisomeric mixture of alcohols M-**14a**,**b** that was not separated but was instead directly silylated with TESCl to provide M-**15a**,**b**. Next, oxidative cleavage and Still−Gennari reaction[15] of the resulting aldehyde provided M-**17a**,**b** as the *Z*-isomer in 65% yield. Conversion of ester **17** to acid M-**18a**,**b** was effected by DIBAL reduction (60%) and oxidation (Dess−Martin, 92%, followed by $NaClO_2$, 90%) rather than standard saponification because of the base sensitivity of this series of molecules. Removal of the TES group with dichloroacetic acid (71%) followed by Dess−Martin oxidation (96%) provided keto acid M-**19a**,**b**, which was smoothly dehydrated to α-pyrone M-**20a**,**b** (87%) upon exposure to acetic anhydride and dichloroacetic acid. DDQ oxidation[16] removed the PMB group (95%),

(8) (a) Negishi, E.; Hu, Q.; Huang, Z. H.; Qian, M. X.; Wang, G. W. *Aldrichimica Acta* **2005**, *38*, 71−88. (b) Huo, S.; Negishi, E.-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. 1, pp 335−408.
(9) Farina, V.; Krishnamurthy, V.; Scott, W. L. *Org. React.* **1997**, *50*, 1−652.
(10) (a) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.
(11) (a) Zhang, W.; Luo, Z.; Chen, C. H. T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443−10450. (b) Fluorous silanes and silica products were purchased from Fluorous Technologies, Inc. DPC owns an equity interest in this company.
(12) (a) Makabe, H.; Higuchi, M.; Konno, H.; Murai, M.; Miyoshi, H. *Tetrahedron Lett.* **2005**, *46*, 4671−4674. (b) Sinha, S.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789−7796.
(13) Afarinka, K.; Vindev, V. *Sci. Synth.* **2003**, *14*, 275−346.
(14) Yang, F. Ph.D. Thesis, University of Pittsburgh, 2006.
(15) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.
(16) Nakajima, N.; Abe, R.; Yonemistu, O. *Chem. Pharm. Bull.* **1988**, *36*, 4244.

Scheme 1. Quasiracemic Synthesis of the Left Fragment



Scheme 2. Premix Stage of the Right Fragment Synthesis



and the resulting alcohol was acetylated as usual to provide allyl acetate M-**21a**,**b** in 100% yield.

Throughout this work, the quasiracemic mixtures were treated like standard racemic mixtures for separation and identification.[7] Relevant chemical shifts and coupling constants in the ^{1}H and ^{13}C NMR spectra of M-**21a**,**b** matched very well with those reported for lagunapyrone B **2**, thereby supporting the assignment of this part of the structure.

The premix stage of the synthesis of right fragment involved asymmetric aldol reaction and tagging, as summarized in Scheme 2. The Evans aldol reaction[17] of (*S*)-**22** with tiglic aldehyde **23** under standard conditions to provide Evans *syn*-aldol adduct (*S*,*S*)-**24** (Bu_2BOTf) was reported to be low yielding by Hamada,[18] and indeed we also experienced problems with this reaction. Hamada reported that the yield of the standard Evans aldol product (*S*,*S*)-**24** could be increased significantly by using $TiCl_4$/^{i}Pr$_2$NEt conditions;[17b] however, in our hands these conditions produced a separable mixture of the non-Evans *syn*-product (*R*,*R*)-**24** (isolated in 66% yield)[19] along with the *anti*-aldol product (*S*,*R*)-**24** (isolated in 9% yield). Only a trace of the expected Evans *syn*-product (*S*,*S*)-**24** (<2%) was formed.

The configuration of (*R*,*R*)-**24** was proved by X-ray crystallography (see Supporting Information). Further, we exchanged spectra with Prof. Hamada and learned that indeed his $TiCl_4$ product was different from ours, not the same. Thus, his structure assignment is also correct, and we currently do not understand why our results and his differ significantly. Nonetheless, because we needed both enantiomers of the aldol adduct and because the conditions proved reliable, we scaled up the synthesis of (*R*,*R*)-**24** and tagged this adduct with a fluorous TIPS triflate bearing the C_3F_7 group to provide (*R*,*R*)-**25a**. Starting from the enantiomer of (*S*)-**22** (not shown), we prepared the enantiomer of (*R*,*R*)-**24** by aldol reaction and then tagged this with the C_4F_9 variant of the fluorous TIPS group to give (*S*,*S*)-**25b**. Quasiracemate M-**25a**,**b** was then made by mixing equal amounts of the corresponding quasienantiomers.

The fluorous mixture synthesis steps to make fragment M-**32a**,**b** are summarized in Scheme 3. Reductive removal of the auxiliary ($LiBH_4$, 70%) from quasiracemate M-**25a**,**b** followed by PCC oxidation (91%) provided M-**26a**,**b**. Allylation with allyl trimethylsilane and dimethylaluminum chloride[20] then provided *anti*,*syn*-M-**27a**,**b** as a single isomer in 78% yield. The 1,3-anti configuration of the diol was confirmed by deprotection of the F-TIPS group to provide a true racemate, followed by

(17) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111. (b) Evans, D. A.; Reiger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.
(18) Makino, K.; Henmi, Y.; Hamada, Y. *Synlett* **2002**, 613−615.
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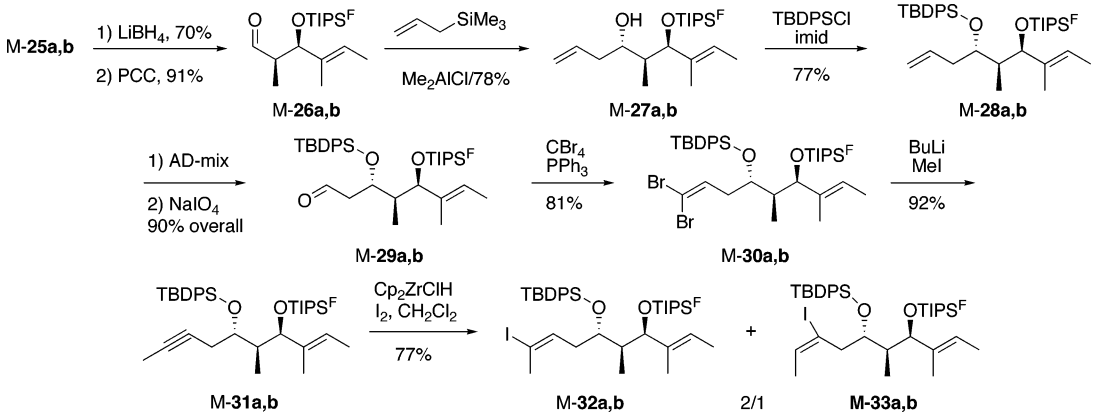
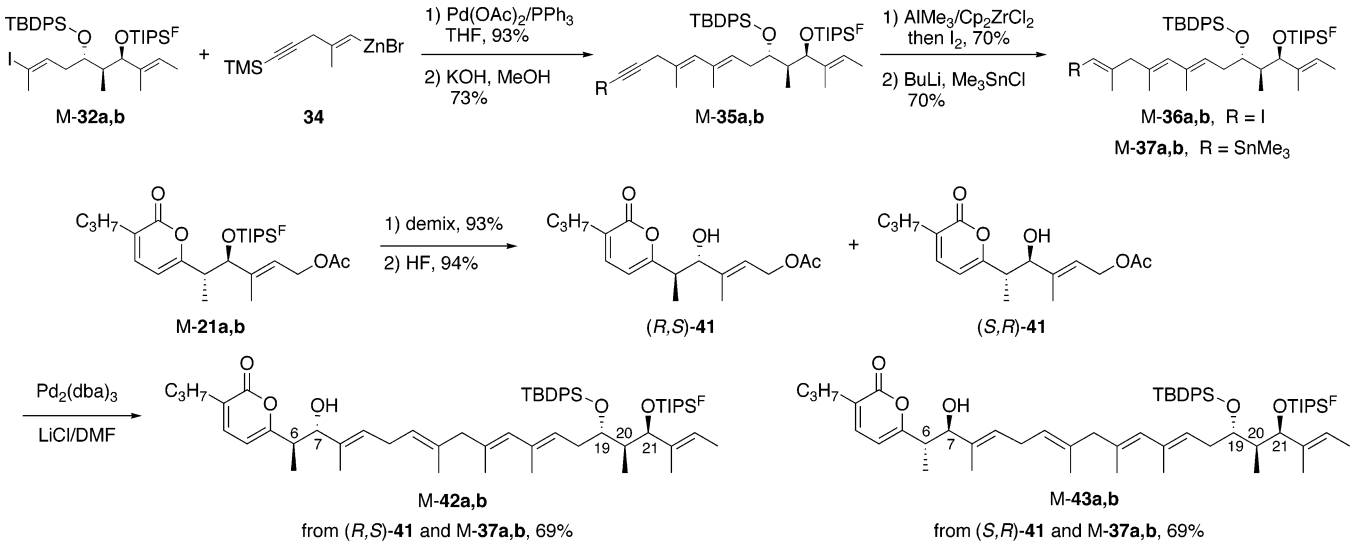
(20) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840−10852.

Scheme 3. Quasiracemic Synthesis of the Right Fragment



Scheme 4. Fragment Coupling To Make Four Protected Lagunapyrones



M-**42a,b** and M-**43a,b** have a single configuration at C6,C7 and both configurations, SSR (shown) and RRS (not shown), at C19–21

conversion to the acetonide and ^{13}C NMR analysis[2] (not shown, see Supporting Information). The data for this analysis were very similar to those reported by Fenical,[1] thereby confirming his assignment of the relative configuration of this part of lagunapyrone.

Protection of alcohol M-**27a**,**b** with TBDPSCl was slow, but after 3 days provided a 77% yield of M-**28a**,**b** alongside 17% of recovered **27**.[21] Regioselective dihydroxylation of M-**28a**,**b** was accomplished with AD-mix-α, and the resulting diol was cleaved to aldehyde M-**29a**,**b** with $NaIO_4$ (95%). Conversion to the dibromide by the Corey−Fuchs method (CBr_4, PPh_3, 81%), followed by treatment with butyllithium and in situ methylation of the resulting anion, provided alkyne M-**31a**,**b** in 92% yield. Hydrozirconation of **31** followed by iodinolysis provided M-**32a**,**b** and M-**33a**,**b** in good yield (77%), but with relative low regioselectivity in favor of **32** (2/1) despite the nearby bulky TBDPS ether. The major regioisomer M-**32a**,**b** was carefully separated by chromatography in preparation for union of the fragments.

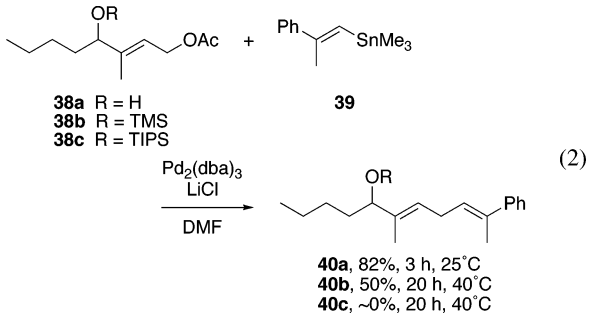
Vinyl zinc reagent **34** was readily available from the corresponding vinyl iodide (see Supporting Information) and served as the lynch pin for fragment coupling (reagent equivalent of **5** in Figure 2) as shown in Scheme 4. Negishi coupling[8] of M-**32a**,**b** and **34** provided a conjugated diene (93%), whose alkynyl silane was then removed with KOH to provide M-**35a**,**b** in 73% yield. Treatment of **35** under standard conditions with Cp_2ZrCl_2 and Me_3Al,[22] followed by iodination of the so-formed intermediate, provided *E*-vinyl iodide M-**36a**,**b** in 70% yield. Halogen−lithium exchange followed by quenching with Me_3-SnCl then provided the corresponding *E*-vinyl stannane M-**37a**,**b**.

Unfortunately, attempted coupling of M-**37a**,**b** with allyl acetate M-**21a**,**b** under a variety of conditions did not result in detectable amounts of the expected four-compound mixture of protected lagunapyrones. Because stannane M-**37a**,**b** coupled with simple model compounds,[14] we began to suspect that the problem was with the fluorous TIPS ether in the allylic position (O7) of allyl acetate M-**21a**,**b**. To probe the effect of this substituent further, we conducted a simple but insightful series of model couplings shown in eq 2. The free alcohol **38a** and its derived TMS **38b** and TIPS **38c** ethers were coupled with vinyl stannane **39** under identical conditions ($Pd_2(dba)_3$, LiCl, DMF). The reaction with free alcohol **38a** was complete in only 3 h at 25 °C and provided **40a** in 82% yield after chromatographic

(21) This sequence of steps was also conducted with a TBS protecting group, and this is described in ref 14 and in the Supporting Information.

(22) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1095−1097.

purification. Reaction of the TMS ether **38b** required 20 h at 40 °C and provided **40b** in only 50% yield, while the experiment with the standard TIPS ether **38c** did not provide any detectable amount of **40c** over 20 h at 40 °C.



(2)

These results pinpoint the problem in the failed couplings of **37** and **21** and, more importantly, suggest an expedient solution. The fluorous TIPS ether group in **21** is the culprit that blocks coupling, but it is apparently the size of the silyl group and not its fluorous substituent that causes the problem. The solution is simply to remove this group before coupling. This adds three reactions to the synthesis because M-**21a**,**b** must be demixed before it is deprotected (two extra reactions because in the original plan all protecting groups were to be removed simultaneously) and coupled (one extra reaction). We deemed that a small price to pay for success.

Demixing of M-**21a**,**b** by preparative fluorous HPLC[23] occurred smoothly to provide quasienantiomers (*R*,*S*)-**21a** and (*S*,*R*)-**21a**, which were then deprotected to provide true enantiomers (*R*,*S*)-**41** and (*S*,*R*)-**41** (Scheme 4). Gratifyingly, individual coupling of (*R*,*S*)- and (*S*,*R*)-**41** with quasiracemate M-**37a**,**b** provided quasi-diastereomeric two-compound mixtures M-**42a**,**b** and M-**43a**,**b** in 60% yield. These were preparatively demixed, and the products were detagged to provide all four target isomers of **2** in individual pure form in amounts ranging from 4.2 to 6.0 mg. The complete structures of these final products are shown in Figure 3 (labeled as **2.1**−**2.4**) along with their optical rotations and the fluorous tagging scheme (for reference).

Carbon-13 and ^{1}H NMR spectra (151 and 600 MHz, respectively) of all four of these stereoisomers were, to the best of our ability to assess, identical. This is expected for two pairs of compounds (**2.1**/**2.4** and **2.2**/**2.3**) because they are enantiomers. However, the spectra of the diastereomeric compounds were also identical, indicating that the long spacer between the remote pairs of stereocenter groups prohibits communication of these groups, at least under these standard NMR recording conditions. Importantly, all of the spectra also matched very well with both the tabulated spectra for lagunapyrone B[1] and the copies of the spectra kindly provided by Dr. Fenical.

Thus, the constitutional and partial stereochemical assignment of **2** by Fenical and co-workers is correct, and there remains only the question of absolute configuration of the fragments. Preferred ways to answer this question are by chiral HPLC analysis or by synthesis of a chiral derivative, but unfortunately, after almost a decade of storage, the remaining natural sample of lagunapyrone B had decomposed. Accordingly, we turned

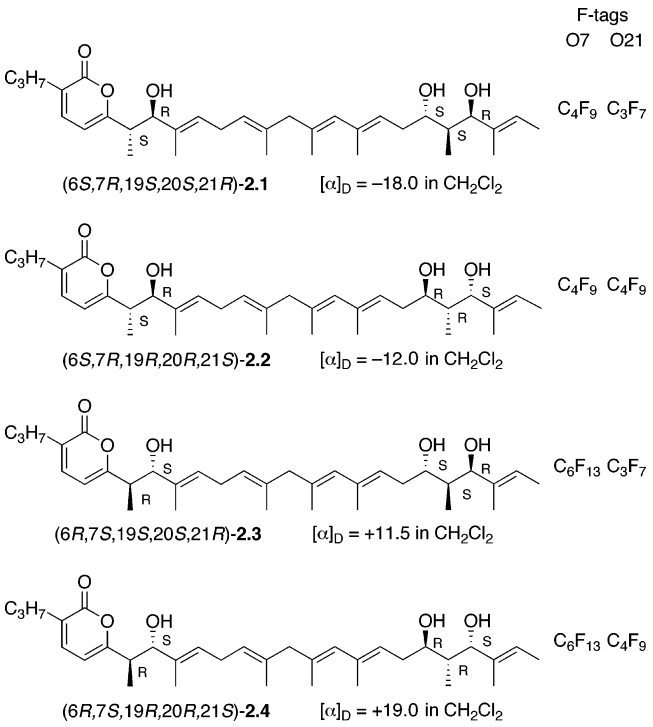


Figure 3. Four candidate structures **2.1**−**2.4** for lagunapyrone with optical rotations (c = 0.2); **2.3** is lagunapyrone.

to polarimetry and measured the optical rotations indicated in Figure 3 under conditions similar to those used for the natural product (CH_2Cl_2, c = 0.2).[24] Enantiomeric pairs gave rotations that were opposite in sign and approximately equal in magnitude, as expected. The rotation of the natural product (+10.9) under these conditions matched very well to that of the 6*R*,7*S*,19*S*,-20*S*,21*R* isomer **2.3** (+11.5), and accordingly we assign this configuration to lagunapyrone B, and, by analogy, to lagunapyrones A and C.

Conclusions

The convergent synthesis of lagunapyrone B described herein requires 18 linear steps starting from the Paterson *anti*-aldol reaction of readily available aldehyde **9**. By using the technique of fluorous quasiracemic synthesis and the "mix early/demix late" principle, most of these steps only had to be conducted once, even though two and ultimately four compounds were being made. The synthesis features key Negishi and Stille couplings of the quasiracemic fragments to a simple lynch pin fragment to build the lagunapyrone backbone in short order. One of the demixings had to be conducted one step earlier than planned because a steric effect of the protecting group shut down the Stille coupling, but the work around by early deprotection was straightforward thanks to the convergent strategy. A new α-pyrone synthesis involving Still−Gennari reaction of a *β*-silyloxyaldehyde to give a *δ*-silyloxy-α,*β*-unsaturated ester, followed by conversion to the *δ*-keto-α,*β*-unsaturated acid and dehydration, was deployed to make the pyrone fragment.

The techniques of quasiracemic synthesis used herein are especially straightforward because the quasiracemic mixtures

(23) Curran, D. P. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 101−127.

(24) Fenical also measured the rotation of lagunapyrone B in CH_2Cl_2 but at c = 3.7. In addition to the rotation measured at c = 0.2 in Figure 3, we also measured two rotations at higher concentrations to probe for possible concentration dependence: **2.3**, $[\alpha]_D$ = +11.5 at c = 0.5; **2.2**, $[\alpha]_D$ = −11.4 at c = 0.4. We thank Mr. X. Wang for conducting these experiments.

typically behave like standard racemic mixtures in standard separation methods and spectroscopic analyses.[7] However, unlike true enantiomers, the quasienantiomers can be separated and identified at any time by using fluorous HPLC techniques. The double tagging method used here (each fragment gets its own fluorous tag) has only been introduced recently in a proof-of-principle publication,[6f] and this is the first example of use of the technique to solve a structural problem. That the tagging and demixing were successful could not be proved by standard spectroscopic analysis because the compounds exhibit substantially identical spectra, but it was clearly shown by optical rotation experiments. The results encourage the continued application and expansion of fluorous mixture synthesis methods for the preparation of natural product stereoisomer libraries.

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Note Added after ASAP Publication. After this paper was published ASAP on September 26, 2006, a third author was added and the Acknowledgment modified accordingly; changes were made to the first sentences of paragraphs 6, 13, and 15 and the first, second, and fourth sentences of paragraph 12 in the Results and Discussion section; and a correction was made to the explanatory text under compound M-**43a**,**b** in Scheme 4. The corrected version was published ASAP on October 5, 2006.

Supporting Information Available: Full experimental details and key characterization data of new compounds; a CIF file of the X-ray crystal structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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