Pergamon

Tetrahedron Letters 40 (1999) 1269–1272

TETRAHEDRON LETTERS

An Improved Synthesis of the (*E,Z*)-Dienoate Precursor of (+)-Damavaricin D Via a Vinylogous Horner-Wadsworth-Emmons Reaction

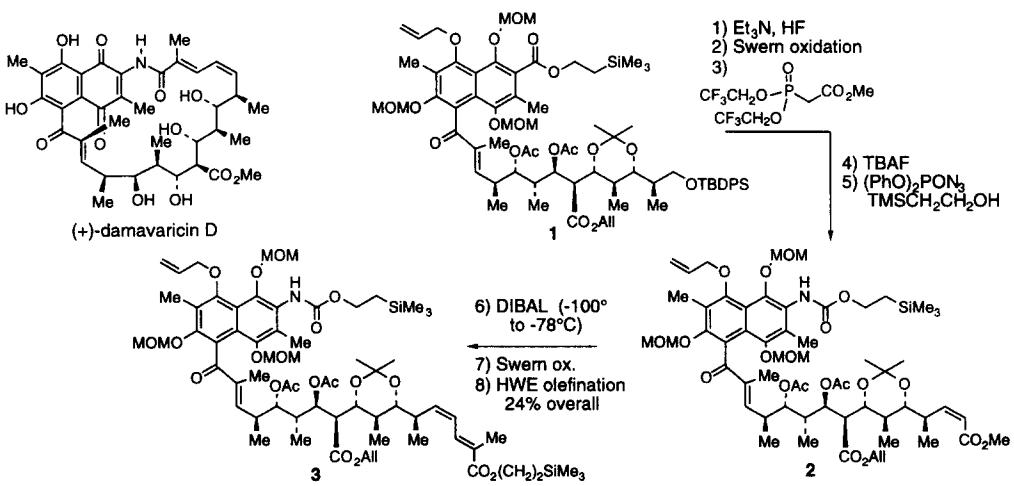
Sherry R. Chemler, D. Scott Coffey and William R. Roush*

Department of Chemistry, University of Michigan, Ann Arbor, MI 48109 and Department of Chemistry, Indiana University, Bloomington, IN 47405

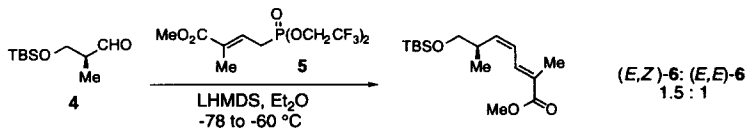
Received 1 December 1998; revised 9 December 1998; accepted 10 December 1998

Abstract: *An improved synthesis of the C(1)-C(5) (E,Z)-dienoate segment of (+)-damavaricin D precursor **3** was accomplished using the unsaturated phosphonate reagent **9** in a (Z)-selective vinylogous Horner-Wadsworth-Emmons reaction.*

In our recently completed total synthesis of (+)-damavaricin D (DmD), the C(1)-C(5) (*E, Z*)-dienoate unit of macrocyclization precursor **3** was installed in 24% overall yield via an eight step sequence starting from **1**.[1] The (*Z*)-enoate unit of **2** was generated with 8 : 1 selectivity using Still's (*Z*)-selective olefination procedure,[2] and the (*E*)-trisubstituted enoate was introduced subsequently by a conventional Horner-Wadsworth-Emmons reaction.[3] The most difficult step of this sequence was the selective DIBAL reduction of **2** that had to be performed under experimentally stringent conditions (THF, -100 °C to -78 °C) in order to minimize competitive reduction of other carbonyl functions in the molecule; the desired allylic alcohol was obtained in 62% yield along with 16% of the corresponding enal after one recycle of recovered starting material.[1] We describe herein the development of a more concise five-step route (30% overall yield) to the key dienoate intermediate **3** involving a (*Z*)-selective vinylogous Horner-Wadsworth-Emmons reaction using the unsaturated phosphonate reagent **9**.



In the early stages of this program we explored the Horner-Wadsworth-Emmons reaction of aldehyde **4** with the unsaturated phosphonate **5** as a route to the targeted (*E,Z*)-dienoate.[4] Our best result at that time was obtained by using LHMDS in Et_2O. However, because these conditions provided the (*E,Z*)-dienoate **6** with only 1.5 : 1 selectivity, we were discouraged from attempting to apply this method to the DmD synthesis.



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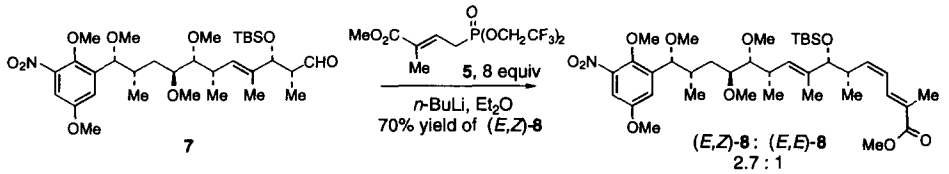
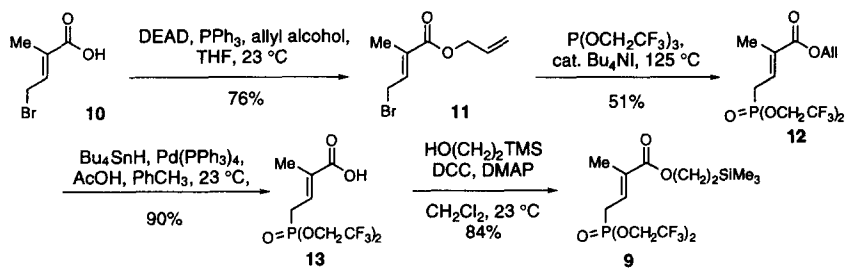
PII: S0040-4039(98)02638-0

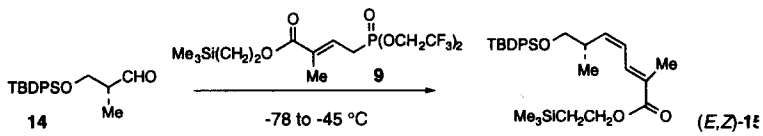
Evans and co-workers subsequently reported a successful application of this methodology in their total synthesis of (+)-macbecin.[5] Although they also obtained low selectivity (1.5 : 1) in the Horner-Wadsworth-Emmons reaction of *i*-PrCHO and **5**, somewhat better selectivity (2.7 : 1) favoring (*E,Z*)-**8** was achieved when macbecin precursor **7** was treated with a large excess (8 equiv) of the anion generated from phosphonate **5**.



This result encouraged us to reexamine the viability of this method as a route to the damavaricin precursor **3**. To do so, however, required that we first develop a synthesis of the unsaturated phosphonate **9** reagent containing a β-trimethylsilylethyl ester protecting group. We had already spent considerable effort orchestrating the protecting group combinations in **3** such that the aniline and carboxylic acid units could be liberated in a single step immediately prior to the macrolactamization reaction, and we did not wish to revisit this aspect of the synthesis.[1] The synthesis of phosphonate **9** thus began with γ-bromotiglic acid **10**, obtained by bromination of tiglic acid as previously described.[6] It was necessary to protect the acid as allyl ester **11** prior to the Arbuzov reaction as trifluoroethyl esters were obtained when acid **10** was used, and the 2-trimethylsilyl ethyl ester of **10** did not survive the Arbuzov conditions (complex mixtures were obtained). Esterification of **10** with allyl alcohol under Mitsunobu conditions[7] afforded **11** (76%), which was then submitted to the Arbuzov reaction with 2,2,2-trifluoroethyl phosphite (10 equiv) in the presence of catalytic Bu_4NI (0.1 equiv), thereby providing phosphonate **12** in 51% yield.[8,9] The allyl group was removed[10] (90%) and the resulting acid **13** was re-esterified with β-trimethylsilylethanol, DCC, and DMAP to provide the targeted phosphonate reagent **9** (84%).

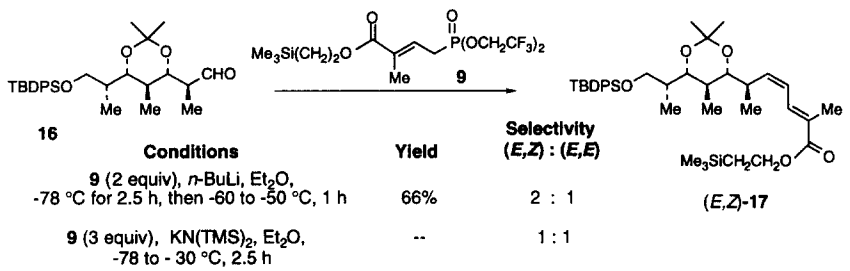


Reactions of phosphonate **9** and aldehyde **14** were explored to develop conditions that maximized selectivity for the (*E,Z*)-diene. Of the various base and solvent combinations examined, best results were obtained by use of potassium hexamethyldisilazide (KHMDS) in Et_2O: this combination provided (*E,Z*)-**15** with 4.7 : 1 selectivity (entry 1). Interestingly, addition of 18-crown-6 to this reaction, which in other systems serves to enhance (*Z*-)selectivity,[2] gave an 1 1 : 1 mixture favoring(*E,E*)-**15** (entry 2). The (*E,E*)-diene also predominated by a significant margin in reactions using MeMgBr as the base (entry 8). Reactions performed using *n*-BuLi to deprotonate **9** were only marginally selective: when performed in Et_2O or toluene (*E,Z*)-**15** was obtined with 1.3-1.6 : 1 selectivity, while the reaction with *n*-BuLi in THF gave a 2 : 1 mixture favoring (*E,E*)-**15**. While the stereoselectivity of the olefination reactions of **14** was insensitive to the number of equivalents of the phosphonate reagent employed (entries 3-5), the stereoselectivity of these reactions is temperature sensitive and best results were obtained when the aldehyde was added slowly to the phosphonate anion at -78 °C over a 0.5 to 1.0 h period.

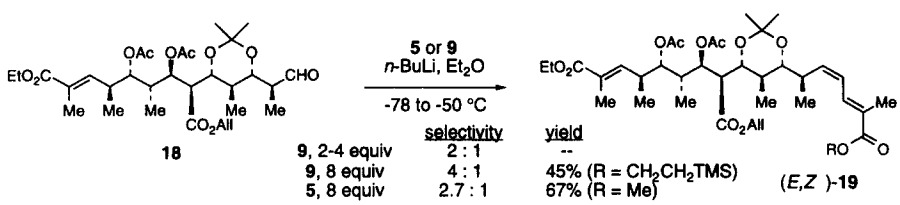


Entry	Equiv 9	Base, Solvent	Selectivity *E,Z* : *E,E*	Yield
1	1.4	KHMDS, Et_2O	4.7 : 1	84%
2	2.9	KHMDS, Et_2O, 18-crown-6	1 : 11	--
3	1.4	*n*-BuLi, Et_2O	1.6 : 1	73%
4	5	*n*-BuLi, Et_2O	1.3 : 1	--
5	8	*n*-BuLi, Et_2O	1.3 : 1	80%
6	5	*n*-BuLi, THF	1 : 2	--
7	5	*n*-BuLi, toluene	1.3 : 1	--
8	2.0	MeMgBr, Et_2O	1 : 9	--

Encouraged by the results obtained in the reaction of **9** and **14**, we explored the olefination reactions of **9** with progressively more complex substrates. However, we were quickly disappointed to discover that the reaction of **9** and **16** was non-selective using KHMDS under the conditions developed for the reaction with **14**. However, a 2 : 1 mixture favoring (*E,Z*)-**17** was obtained using 2 equiv of **9** with *n*-BuLi as the base. When the olefination of **18** was performed using 2-4 equiv of **9**, (*E,Z*)-**19** was also obtained with 2 : 1 selectivity. Fortunately, selectivity in this case increased to 4 : 1 when **18** was treated with 8 equiv of the anion generated from **9**. Under these conditions, (*E,Z*)-**19** was obtained in 45% yield along with 32% of aldehyde **18** which could be recycled. Interestingly, the olefination of **18** with phosphonate reagent **5** under comparable conditions provided a 2.7 : 1 mixture of (*E,Z*) : (*E,E*) olefin isomers, suggesting that further modification of the ester unit may constititute a strategy to increase the stereoselectivity of these Horner-Wadsworth-Emmons reactions.



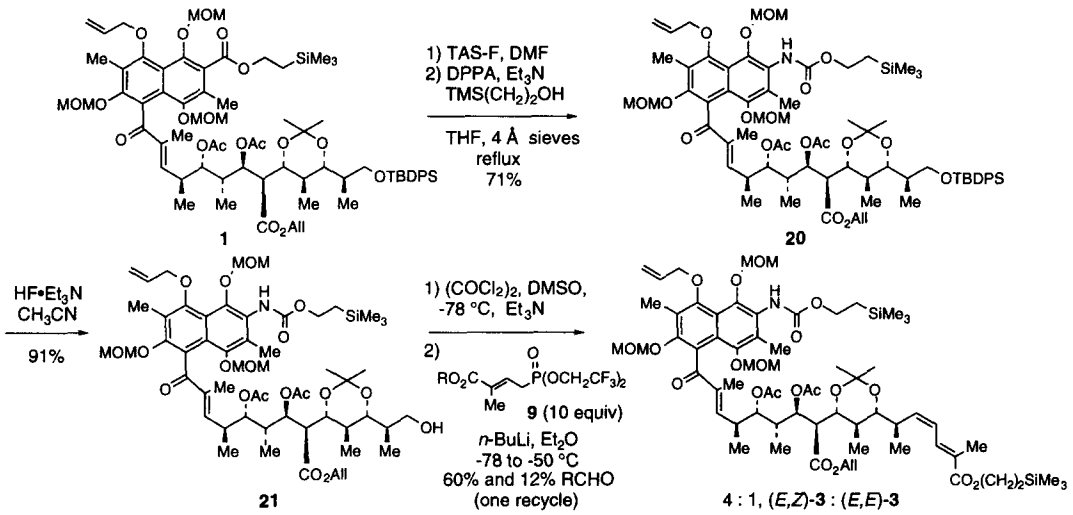
Conditions	Yield	Selectivity (*E,Z*) : (*E,E*)
9 (2 equiv), *n*-BuLi, Et_2O, -78 °C for 2.5 h, then -60 to -50 °C, 1 h	66%	2 : 1
9 (3 equiv), $KN(TMS)_2$, Et_2O, -78 to - 30 °C, 2.5 h	--	1 : 1



	selectivity	yield
9, 2-4 equiv	2 : 1	--
9, 8 equiv	4 : 1	45% (R = CH_2CH_2TMS)
5, 8 equiv	2.7 : 1	67% (R = Me)

Application of this methodology to an improved synthesis of **3** proceeded as follows. The carbamate functionality of **20** was introduced in 71% yield via a Curtius rearrangement[11] of the carboxylic acid generated by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F, 2.2 equiv) mediated selective deprotection[12] of **1**. Treatment of **20** with HF•Et_3N in refluxing CH_3CN afforded primary alcohol **21** (91%), which was subsequently oxidized using Swern conditions[13] to the corresponding aldehyde. Horner-Wadsworth-Emmons olefination of the crude aldehyde with 10 equiv of the lithium anion of **9** in Et_2O afforded, after one recycle of the recovered aldehyde intermediate, 60% of a 4 : 1 mixture of (*E,Z*) : (*E,E*) dienoates **3** along with 13% of recovered

aldehyde. The desired DmD intermediate, (*E,Z*)-**3** was isolated in 47% yield by HPLC, and proved to be identical in all respects to the intermediate utilized in our DmD total synthesis.[1] This five step sequence thus provides DmD intermediate **3** in 30% overall yield from **1**.



In summary, we have developed an improved synthesis of DmD intermediate **3** from precursor **1** using the vinylogous Horner-Wadsworth-Emmons reagent **9** in a (*Z*)-selective olefination sequence. Although it is not clear at present to what extent the reaction stereoselectivity of these vinylogous Horner-Wadsworth-Emmons reactions is governed by kinetic or thermodynamic considerations,[5,14] it is clear that synthetically useful results may be obtained by judicious selection and optimization of reaction conditions.

Acknowledgment. Support provided by the National Institutes of Health (GM 38436) is gratefully acknowledged.

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