methyl bromodifluoroacetate, 683-98-7; isopropyl bromodifluoroacetate, 134682-34-1; copper, 7440-50-8; 1-hexene, 592-41-6; 1-heptene, 592-76-7; trimethylvinylsilane, 754-05-2; 1-octene, 111-66-0; 5,6-epoxy-1-heptene, 10353-53-4; 9-decanol, 13019-22-2; 5-hexen-2-one, 109-49-9; ethyl 2-methyl-4-pentanoate, 53399-81-8; diethylallylphosphonate, 1067-87-4; diethyl (1,1-difluoro-3-butenyl)phosphonate, 80077-71-0; cyclohexene, 110-83-8; 3-octene, 592-98-3; diallyl ether, 557-40-4.

Supplementary Material Available: ^{1}H, ^{19}F, and ^{13}C NMR spectra for all relevant compounds (32 pages). Ordering information is given on any current masthead page.

Cyclization of 9-Substituted Decanoic Acid Derivatives to 9-Decanolide and 9-Decanelactam

Martí Bartra* and Jaume Vilarrasa*

Department of Organic Chemistry, Faculty of Chemistry, University of Barcelona(III), 08028 Barcelona, Catalonia, Spain

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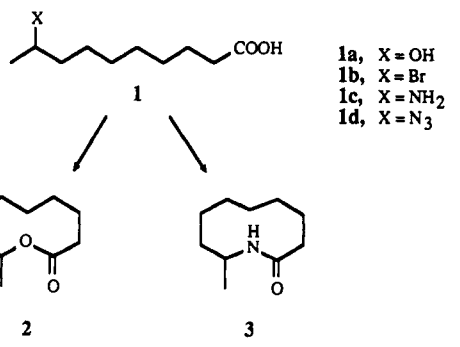
Several standard and some novel cyclization reactions have been applied to 9-substituted decanoic acids to establish which are the optimum procedures for lactonization and lactamization at 80 °C under identical high-dilution conditions. The methods of Galli-Mandolini and Kellogg (cyclization of 9-bromodecanoate ion), Gerlach (cyclization of *S*-2-pyridyl 9-hydroxydecanethioate in the presence of $AgClO_4$), and Yamaguchi (activation of the carboxyl group as a mixed anhydride) in the presence of an excess of DMAP appear to be the most useful for the preparation of the 10-membered lactone, phoracantolide I, under these conditions. Analogously, treatment of *S*-2-pyridyl 9-azidodecanethioate with $Sn(SePh)_3^-$ afforded the best yield of the 10-membered lactam. The mixed anhydrides RCOOCOAr (Ar = 2,4,6-trichlorophenyl) are more reactive than thioesters RCOSPy (Py = 2-pyridyl) with benzyl alcohol or benzylamine; it is confirmed that the addition of DMAP activates the reaction of alcohols with mixed anhydrides much more than with pyridyl thioesters, while the addition of Ag^+ strongly activates RCOSPy in relation to either RCOOCOAr or $RCOOSO_2Mes$.

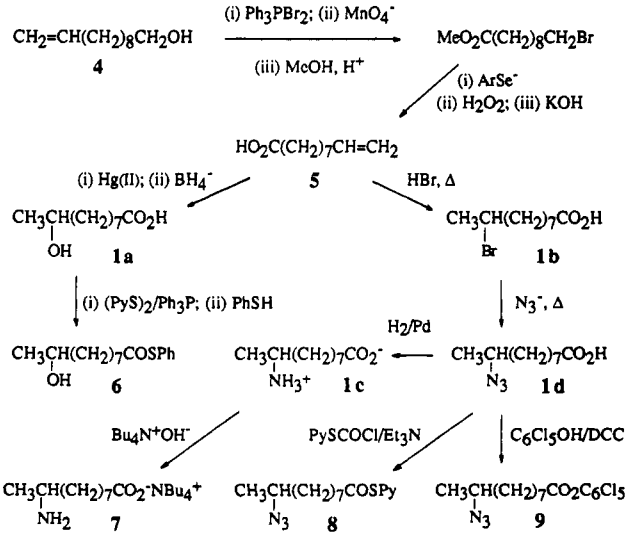
In connection with a research project aimed at preparing modified macrolides of potential therapeutic interest, we focused our attention on relevant lactonization and lactamization procedures[1] developed in the past two decades to perform the crucial step in the synthesis of these and related natural products. Rather than checking randomly some of these methods on our modified secoerythronolides,[2] we considered that a comparison under similar conditions on a much more readily available substrate would be more useful. Thus, we chose a set of 9-substituted decanoic acids 1, which could afford (±)-phoracantolide I (9-decanolide, 2)[3] or its analogue 2-aza-3-methylcyclodecanone (9-decanelactam, 3), because of their simplicity, but also because their cyclization was a challenge since, as it is well-known, the formation of medium-sized rings is much more difficult than that of smaller and larger cyclic compounds (Scheme I).

We report here our results—percentages of monomers 2 and 3 and the corresponding cyclic dimers—at 80 °C in all cases under identical high-dilution conditions. Thus, we have compared the relative cyclization rates of substrates 1, usually after conversion of their COOH groups into different, more reactive carboxyl derivatives.

Scheme I



Scheme II



Several routes to 9-hydroxy-, 9-bromo-, 9-amino-, and 9-azidodecanoic acid (1a–d) can be envisaged starting from available substances such as 10-undecenoic acid or 10-

(1) For reviews, see: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Ibid.* **1977**, *33*, 3041. (d) Paterson, I.; Mansuri, M. M. *Ibid.* **1985**, *41*, 3569. (e) Boeckmann, R. K.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7. (f) For a review of the classical methods of lactamization, see: Kopple, K. D. *J. Pharm. Sci.* **1972**, *61*, 1345. Also see: Brady, S. F.; Varga, S. L.; Freidinger, R. M.; Schwenk, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101.

(2) Urpí, F. Doctoral Thesis, University of Barcelona, 1988.

(3) Isolation of phoracantolide I: (a) Moore, B. P.; Brown, W. V. *Aust. J. Chem.* **1976**, *29*, 1365. Very recent syntheses: (b) Fouque, E.; Rousseau, G. *Synthesis* **1989**, 661. (c) Cossy, J.; Pete, J. P. *Tetrahedron Lett.* **1986**, *27*, 2369; *Bull. Chem. Soc. Fr.* **1988**, 989. (d) Bienz, S.; Hesse, M. *Helv. Chim. Acta* **1987**, *70*, 2146. For earlier syntheses, cf.: (e) Suginome, H.; Yamada, S. *Tetrahedron* **1987**, *43*, 3371. (f) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, 1984.

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Table I. Cyclizations to 2 or 3 at 80 °C under High-Dilution Conditions[a]

entry	substrate	previous activation	cyclization cond: other reagent(s)	cyclization cond: solvent	lit. ref	yield (%): monomer	yield (%): dimer
			Lactonization Methods				
1	1a	PySSPy[b]/Ph_3P	$AgClO_4$	benzene	7a	50	25
2	1a	PySSPy/Ph_3P	DMAP	benzene	7b, 6	≈0	≈0
3	1a	ImSSIm[c]/Ph_3P		benzene	8	≈0	≈0
4	6[d]		$AgOCOCF_3$	benzene	9	5	25
5	1a		2-Cl-1-MePy$^+$[e]/Et_3N	CH_3CN	10	10	20
6	1a	ArCOCl[f]/Et_3N	DMAP	benzene	11, 6	30	40
7	1a		DMAP/TFA,[g] DCC	$ClCH_2CH_2Cl$	12	10	15
8	1a		Ph_3P/DEAD	toluene	13	≈0	≈0
9	1a		Ox_2POCl,[h] Et_3N	benzene	14	≈5	≈5
10	1a		Bu_2SnO	toluene	18a,b	≈0	≈0
11	1b		Cs_2CO_3	DMF	19	40	5
12	1b		K_2CO_3	DMSO	20	55	10
			Lactamization Methods				
13	1c		Bu_2SnO	xylene	18a,b	≈0	≈0
14	1c	$(PhO)_2PON_3$, Et_3N	DMAP	benzene	21, 1f	≈0	≈0
15	1c		Ox_2POCl, Et_3N	toluene	22, 14a	≈0	≈0
16	1c	C_6Cl_5OH, DCC		pyridine	23	≈0	≈0
	1c	C_6Cl_5OH, DCC	DMAP	pyridine		≈0	≈0
17	7		$MesSO_2Cl$,[i] $EtPr^i2N$	benzene	24, 22	10	25
	7		$MesSO_2Cl$, DMAP	benzene		10	25
18	8		Sn(II)/PySH/Et_3N	CH_3CN	25	20	25
19	8		PhSeH, Et_3N	CH_3CN		30	40
20	8		$Et_3NH^+Sn(SePh)_3^-$	CH_3CN		45	25
	8		$Sn(SePh)_3^-$, DMAP	CH_3CN		45	25
21	9		$Et_3NH^+Sn(SePh)_3^-$	CH_3CN		45	20

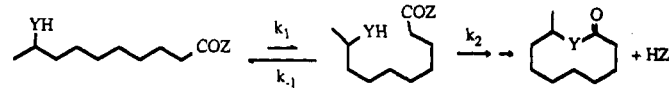
[a] One mmol of substrate, after a previous activation when necessary (usually with 1.1–1.5 equiv of the reagents indicated), in 20 mL of solvent was added through a syringe pump during 6 h to a cyclization flask containing 100 mL of solvent at 80 °C and, in most cases, 10 equiv of "other reagent(s)"; heating was further maintained for 1 h. Most of the cyclizations were repeated three times, with practically constant yields. See the Experimental Section for more details. [b] 2,2'-Dipyridyl disulfide. [c] Bis(4-*tert*-butyl-1-isopropyl-2-imidazolyl) disulfide. [d] Prepared from 1a as indicated in Scheme II. [e] 2-Chloro-1-methylpyridinium iodide. [f] 2,4,6-Trichlorobenzoyl chloride. [g] DMAP plus 4-(dimethylamino)pyridinium trifluoroacetate. [h] 3,3'-(Chlorophosphoryl)bis(1,3-oxazolidin-2-one), sometimes called BOPCl. [i] Mesitylenesulfonyl chloride.

undecen-1-ol (4). In practice, we have converted compound 4 to the common precursor 9-decenoic acid (5)[4] by an indirect shortening of the chain. The optimum conditions are summarized in Scheme II and described in the Experimental Section. We have also obtained a sample of 5 in 85% yield by oxidation, with CrO_3 in aqueous AcOH, of the available, but much more expensive, 9-decen-1-ol.

The cyclization results are shown in Table I. Obviously, we did not attempt to compare all the methods reported so far but instead chose to study a representative selection that included the more common ones. In certain cases for which comparable results exist in the literature, the yields here reported should not be viewed as a correction of (or an improvement with regard to) the former results. In fact, some methods that work well for the preparation of certain macrocyclic rings under the original literature conditions cause polymerization of 1 under the conditions studied here.[5] It is finally to be noted that, in view of the very recent papers of Yonemitsu et al.[6] in which the beneficial effect of an excess of DMAP in the cyclization of secoerythronolide A was clearly demonstrated, we have repeated several of our experiments in the presence of large amounts of DMAP; these results are also shown in Table I.

Among the different methods of lactonization shown in Table I, which are based on the attack of a hydroxy group

Scheme III



on an activated carboxyl derivative (entries 1–9),[7-14] that of Gerlach (entry 1),[7a] in which the carboxyl group is activated as its 2-pyridyl thioester[15] (as in the Corey–Nicolaou method[7b] but in the presence of Ag^+), afforded the highest yield of monomer under the indicated conditions, followed by Yamaguchi's method[11a] in the presence of an

(4) Black, H. K.; Weedon, B. C. L. *J. Chem. Soc.* **1953**, 1785.

(5) For example, a 6-h addition period and 80 °C have been chosen here, when we could have lengthened the addition time to 48 h and looked for the most appropriate temperature for each method (on each substrate), but in such a case we would have not been able to distinguish so clearly among thioesters, mixed anhydrides, active esters, etc. regarding the activation of the carboxyl group vs the attack of OH and NH_2 groups.

(6) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7; *Tetrahedron* **1990**, *46*, 4613. Also see: Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569.

(7) (a) Gerlach, H.; Thalman, A. *Helv. Chim. Acta* **1974**, *57*, 2661. Phoracantolide I was then synthesized in the same lab (in 71% reported yield) by means of this methodology: Gerlach, H.; Künzler, P.; Oertle, K. *Ibid.* **1978**, *61*, 1226. (b) For the direct cyclization (without adding $AgClO_4$) of *S*-2-pyridyl thioesters, usually at higher temperatures, see: Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(8) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409.

(9) (a) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. (b) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *Ibid.* **1977**, *99*, 6756.

(10) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. Also see: Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36.

(11) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. For similar anhydride-based activations, see: (b) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1983**, *48*, 759. (c) Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 2409. (d) Hernández, R.; Rivera, A.; Suárez, E.; Prangé, T. *J. Org. Chem.* **1989**, *54*, 5343.

(12) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896. Also see: Boden, E. P.; Keck, G. E. *Ibid.* **1985**, *50*, 2394.

(13) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455.

(14) (a) Diago, J.; Palomo, A. L.; Fernández, J. R.; Zugaza, A. *Synthesis* **1980**, 547. (b) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818.

(15) Mukaiyama, T.; Matsueda, R.; Suzuki, M. *Tetrahedron Lett.* **1970**, 1901.

excess of DMAP (entry 6).[6] With most of the remaining methods the cyclization of the derivatives of **1a** was slower, so that the final mixtures mainly contained polymeric compounds and/or starting material.

Assuming that the barriers to reach the appropriate conformation for cyclization are similar in all cases, only the relative rate of attack of the nucleophile on the activated carboxyl derivative should be relevant for the present comparisons. In principle, the more electrophilic this carbonyl carbon is, the more readily the substrate will cyclize,[16] thus rapidly decreasing its concentration and maintaining the desired high-dilution conditions (which of course favor the unimolecular cyclization over the bimolecular dimerization). In the presence of Ag^+ ions, it appears that 2-pyridyl thioesters cyclize more readily than the other thioesters and mixed anhydrides. However, in the absence of Ag^+ and in the presence of DMAP, the mixed anhydrides RCOOCOAr (Ar = 2,4,6-trichlorophenyl) are more active than the corresponding RCOSPy.

We have confirmed these observations and the results of Yonemitsu et al.[6] in the following way: (a) when 2,4,6-trichlorobenzoic 10-undecenoic anhydride (**10**) and *S*-2-pyridyl 10-undecenethioate (**11**) were treated (ca. 0.04 M benzene solutions at rt for 2 h) with equivalent amounts of benzyl alcohol and Et_3N, 50% and 10% yields of the expected benzyl 10-undecenoate (**12**) were obtained respectively; (b) in the presence of DMAP (3 equiv), **10** reacted immediately with benzyl alcohol under the same conditions whereas **11** required ca. 45 min, both to give ester **12**; (c) by contrast, in the presence of $AgClO_4$ (3 equiv), **10** gave rise to **12** smoothly (over 1 h) whereas **11** disappeared within 10 min to afford **12** quantitatively. In short, the presence of DMAP activates the reaction of **10** with benzyl alcohol more effectively than that of **11**, while, as expected, the presence of Ag^+ activates **11** in relation to **10**.

$CH_2{=}CH(CH_2)_8COOCOC_6H_2Cl_3$
10

$CH_2{=}CH(CH_2)_8COSPy$
11

$CH_2{=}CH(CH_2)_8COOCH_2Ph$
12

It is worth noting that the requirement of metallic ions to accelerate the lactonization, as in Gerlach's method,[7a] may be a handicap in polyfunctional substrates, since undesired reactions may occur.[17] In these cases, the reagents and conditions shown in entries 2–3 and 5–9, whose usefulness has been proved several times, deserve to be recommended. As shown here, the problem is that most of them are not appropriate for the cyclization of recalcitrant substrates like **1a**, i.e., for the formation of medium-sized rings.

Whereas dibutyltin oxide was not efficient as cyclization agent[18] for **1a** (Table I, entry 10), the direct intramolecular S_N2-like substitution of the carboxylate for the bromide anion, from **1b**,[19,20] gave the best yields of lactone when carried out in DMSO (entry 12). Leaving groups better than bromide are not recommended because we noticed that large amounts of elimination products (olefins) were formed. Thus, it appears, surprisingly, that the simplest methodology produces the highest yield of monomeric product (see Table I). The irreversible character of this intramolecular reaction with an S_N2-like transition state, as compared to the probably reversible attack of the alcohol to the activated carboxyl group with a more congested transition state, may explain its practical advantage in the present case. However, if the substrates contain either functional groups incompatible with this basic medium or stereogenic centers subject to epimerization, this method would not be attractive.

Regarding the macrolactamization, we have investigated several reported methods starting from **1c**, **7**, or **8** (entries 13–18)[18,21–25] and some new variants starting from azides **8** or **9** (entries 19–21). The acyl azide and related methods used commonly in peptide chemistry[1f] have not been systematically evaluated because they require reaction at rt or below, due to the otherwise alternative decomposition of the carboxyl derivative; under these conditions no cyclization is observed even after days with substrates of high conformational mobility like the present ones. Among the methods reported in Table I, those that employ benzeneselenol complexes of Sn(II) as in situ reducing agents of the azide group of **8** and **9** are remarkable. There is little difference between the activation of the carboxyl as the 2-pyridyl thioester **8** or the perchlorophenyl ester **9**, a fact that may be due to the PhSe/PyS and PhSe/C_6Cl_5O substitutions that take place, as we have confirmed by independent experiments.[26] Therefore, reduction with $Sn(SePh)_3^-$ followed by in situ cyclization of azido esters **8**, **9**, or $CH_3CH(N_3)(CH_2)_7COSePh$ is at present the best method to obtain lactam **3**. Nevertheless, the presence of an excess of Sn complexes in the medium (which might promote undesired reactions in polyfunctional substrates), the acidity of PhSeH (which could partially protonate the amine generated in situ if a tertiary amine is absent), and difficulties found in the workup (due to the reagent excess) are potential shortcomings of this method.

From entries 17 and 20, it appears that the use of DMAP instead of a tertiary aliphatic amine has no significant effect on the corresponding lactamization yields. In order to further explore this result, we have compared the reactions of **10**, **11**, and mesitylenesulfonic 10-undecenoic anhydride (**13**) with benzylamine at 0 °C under dilute

(16) As a reasonable hypothesis, we assume that this cyclization reaction, summarized in Scheme III, is very sensitive to the ratio between k_2 and k_{-1}; probably both steps are rate limiting ($k_2 \approx k_{-1}$) for Z groups of moderate electron-withdrawing character, whereas $k_2 \gg k_{-1}$ (i.e., $k_{obs} \approx k_1$) for Z = $SPyAg^+$ and $k_2 \ll k_{-1}$ (i.e., $k_{obs} \approx K_1k_2$) for the weaker electron-withdrawing Z groups.

(17) It has been earlier attributed to this fact the failing of some cyclization attempts: Woodward, R. B., et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213.

(18) (a) Steliou, K.; Szczygielska-Nowosielka, A.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578. (b) Steliou, K.; Poupart, M. A. *Ibid.* **1983**, *105*, 7130. (c) For a related method, see: Otera, J.; Yano, T.; Himeno, Y.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 4501.

(19) (a) Kruizinga, W. H.; Kellog, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183. (b) Barbier, M. *J. Chem. Soc., Chem. Commun.* **1982**, 668. Cyclization of the *O*-mesyl derivative of **1a** (Cs_2CO_3, DMF, 4 days, 40 °C) was reported to give 45% of monomer and 25% of dimer; with K_2CO_3, under the same reaction conditions, yields of 24% of monomer and 45% of dimer were obtained. (c) For a related method, see: Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030.

(20) (a) Galli, C.; Mandolini, L. *Gazz. Chim. Ital.* **1975**, *105*, 367; *Org. Synth.* **1978**, *58*, 98. (b) For related variants, see: Cameron, A. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 161. (c) Karim, M. R.; Sampson, P. *J. Org. Chem.* **1990**, *55*, 598.

(21) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

(22) Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378.

(23) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498; *Ibid.* **1988**, *53*, 487.

(24) (a) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916. (b) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *Ibid.* **1980**, *102*, 1439.

(25) Bartra, M.; Bou, V.; Garcia, J.; Urpí, F.; Vilarrasa, J. *J. Chem. Soc., Chem. Commun.* **1988**, 270.

(26) (a) Romea, P.; Vilarrasa, J. Unpublished results. (b) We have also observed that **10** reacts quickly with PhSeH/Et_3N at rt (PhSe/ArCOO substitution); thus, it is nonsense to prepare analogues of **8** and **9** with more electrophilic CO groups to submit them to lactamization under the conditions of entries 19–21.

conditions, followed by treatment with aqueous HCl after 5 min. In the presence of 3 equiv of Et_3N, 80, 66, and 75% yields of *N*-benzyl-10-undecenamide (14) were obtained from 10, 11, and 13, respectively, while in the presence of 3 equiv of DMAP the respective yields were 100, 90, and 100%. Thus, substitution of DMAP for Et_3N shows a relatively small effect, probably because benzylamine is sufficiently reactive by itself (compared to benzyl alcohol). The absence of a significant rate enhancement from the DMAP additive in the lactamizations of entries 17 and 20 may be explained if one of the steps to the preceding attack of the amine group on the carboxyl derivative (e.g., in entry 20 the azide reduction and/or the conformational equilibrium) is rate limiting, a quite reasonable possibility.

$CH_2{=}CH(CH_2)_8COOSO_2Mes$
13

$CH_2{=}CH(CH_2)_8CONHCH_2Ph$
14

Finally, we have checked the effect of $AgClO_4$ on the reaction of 11 with benzylamine: addition of Ag^+ caused no change in the rate of formation of carboxamide 14 (although it was slower than in another experiment in which only Et_3N was added). Probably, the activation of SPy by Ag^+ is comparable to the deactivation of the amine due to its coordination to the remaining silver ions.

In summary, when the substrate has or may readily adopt a noncongested, appropriate conformation[27] for direct cyclization, most methods reviewed in Table I and others[28] are or should be satisfactory; the choice of the most suitable one will depend on the sensitivity of the protective groups to the cyclization conditions and/or the availability of the precursors and reagents. However, *for more reluctant substrates* having no functional incompatibilities, the intramolecular carboxylate attack on the bromo-substituted carbon atom,[19a,20a] the activation of the carboxyl group as pyridyl thioester (and then adding Ag^+),[7a] and the Yamaguchi method[11] (under Yonemitsu's conditions),[6] appear to afford better yields of lactone under the conditions used in this work, while the methodology based on the reduction and in situ cyclization of a carboxyl-activated azido acid is recommended for macrolactam formation as a general method, among those evaluated here.

Experimental Section

Melting points are uncorrected. Thermally stable oils were purified by Kugelrohr-like distillation. The ^1H and ^{13}C NMR spectra were obtained at 200 and 50.3 MHz, respectively. All the cyclizations were carried out under Ar, and all the solvents employed were rigorously anhydrous. Merck TLC aluminum sheets of silica gel 60 F_{254} and SDS silica gel for flash column chromatography (0.040–0.060 mm) have been used for all over the work.

11-Bromo-1-undecene. Prepared according to ref 29a: Bromine (3.3 mL, 64.5 mmol) was added to a stirred solution of Ph_3P (16.9 g, 64.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C. Then, a solution of 10-undecen-1-ol (10 g, 58.7 mmol) and pyridine (4.7 mL, 58.7 mmol) in CH_2Cl_2 (50 mL) was slowly added. After stirring for 4 h at rt, washing with water, drying of the organic layer, and removal of the solvent in vacuo (rotary evaporator), there was obtained a residue that was treated with hexane (to eliminate Ph_3PO). Evaporation of the filtrate afforded 13.2 g (97%) of 11-bromo-1-undecene: oil; bp 60 °C (0.075 mmHg) [lit.[29b] bp 95–98 °C (2 mmHg)]; ^1H NMR ($CDCl_3$) δ 1.0–2.1 (m, 16 H), 3.39 (t, *J* = 6.8, 2 H), 4.92 (ddt, *J* = 10.1, 2.2, 1.2, 1 H), 4.97 (ddt, *J* = 17.1, 2.2, 1.5, 1 H), 5.80 (ddt, *J* = 17.2, 10.1, 6.6, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.2, 28.8, 28.9, 29.1, 29.4, 29.4, 32.9, 33.9, 34.1, 114.4, 139.5; IR (film) 3090, 1640 cm^{-1}.

10-Bromodecanoic Acid. Prepared according to ref 29c: A solution of 11-bromo-1-undecene (10 g, 43 mmol) and $Bu_4N^+Br^-$ (1.6 g, ca. 5 mmol) in benzene (75 mL) was added to a solution of $KMnO_4$ (16 g, ca. 100 mmol) in water (60 mL) at 0 °C. The mixture was vigorously stirred for 6 h at rt. After the excess of $KMnO_4$ was destroyed with $NaHSO_3$ and 3 M HCl was added, the layers were separated and the aqueous one was extracted again with benzene. Finally, the combined organic layers were washed with 1 N HCl, dried, and evaporated to give 9.92 g (92%) of 10-bromodecanoic acid as a white solid: mp 38–40 °C (lit.[29d] mp 37–38 °C); ^1H NMR ($CDCl_3$) δ 1.1–1.9 (m, 14 H), 2.33 (t, *J* = 7.5, 2 H), 3.38 (t, *J* = 6.8, 2 H), 10.0 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.2, 28.7, 29.0, 29.2, 29.3, 32.8, 34.1, 34.2, 181.2; IR (film) 3400–2600, 1715 cm^{-1}.

Methyl 10-Bromodecanoate. 10-Bromodecanoic acid (5 g, 19.9 mmol) and TsOH (ca. 200 mg) were stirred at rt for 24 h in anhydrous MeOH (50 mL). After evaporation of MeOH in vacuo, the residue was solved in CH_2Cl_2. The resulting organic solution was washed with water, dried, and evaporated in vacuo to give 4.96 g (94%) of methyl 10-bromodecanoate: oil; bp 170 °C (20 mmHg) [lit.[29e] bp 165 °C (12 mmHg)]; ^1H NMR ($CDCl_3$) δ 1.1–1.9 (m, 14 H), 2.31 (t, *J* = 7.5, 2 H), 3.38 (t, *J* = 6.7, 2 H), 3.66 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.2, 28.7, 29.0, 29.2, 29.3, 32.8, 34.0, 34.1, 51.2, 174.5; IR (film) 1740 cm^{-1}.

Methyl 9-Decenoate. Prepared according to ref 29f: *o*-Nitrophenyl selenocyanate (320 mg, 1.42 mmol), in absolute EtOH (5 mL) at 0 °C, was treated with $NaBH_4$ (70 mg, 1.85 mmol) under N_2. Methyl 10-bromodecanoate (315 mg, 1.17 mmol) in THF (1 mL) was added, and stirring under N_2 was maintained for 8 h at rt. The solution was diluted with THF (5 mL), was cooled again at 0 °C, and was treated with 30% H_2O_2 (1 mL). After stirring for 6 h at rt, hexane and water were added. The organic layer was separated, washed (aqueous $NaHCO_3$, then aqueous NaCl), dried, and evaporated. Purification of the residue by column chromatography (CH_2Cl_2) afforded 140 mg (65%) of methyl 9-decenoate: oil; bp 120 °C (20 mmHg) [lit.[29g] bp 123 °C (21 mmHg)]; ^1H NMR ($CDCl_3$) δ 1.1–2.1 (m, 12 H), 2.30 (t, *J* = 7.7, 2 H), 3.66 (s, 3 H), 4.9–5.9 (m, spin system as in 11-bromo-1-undecene, 3 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 28.6, 28.7, 28.8, 29.0, 33.5, 33.8, 51.2, 114.2, 139.1, 174.4; IR (film) 1740 (s), 1640 (w) cm^{-1}.

9-Decenoic Acid (5). Methyl 9-decenoate (600 mg, 3.26 mmol) was treated with KOH (650 mg, 9.8 mmol) in a mixture of THF (10 mL) and water (5 mL) for 14 h at rt. After acidification with 3 N HCl, Et_2O (ca. 50 mL) was added. The two phases were separated, and the aqueous one was extracted twice more. The organic solutions were washed with 1 M HCl, dried, and evaporated to afford 500 mg (90%) of 5: oil; bp 140 °C (0.15 mmHg)

(27) The significance of conformational effects in the cyclization of seco acids to macrolide antibiotics was early stressed by several authors; see, e.g.: (a) Masamune, S.; Khim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Reference 17. (c) Stork, G.; Rychnovsky, D. *Pure Appl. Chem.* **1987**, *59*, 345; *J. Am. Chem. Soc.* **1987**, *109*, 1565.

(28) For other direct macrolactonization methods not evaluated in this paper, see inter alia (a) 1-Phenyl-2-tetrazoline-5-thione plus *tert*-butyl isocyanide: Schmidt, U.; Dietsche, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 771. (b) Triacylamine method: Wasserman, H. H.; Gambale, R. J.; Pulwer, M. J. *Tetrahedron Lett.* **1981**, *22*, 1737. Also see: Wasserman, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845. (c) Triphase catalytic cyclization: Regen, S. L.; Kimura, Y. *J. Am. Chem. Soc.* **1982**, *104*, 2064. (d) Enol esters: Gais, H. J. *Tetrahedron Lett.* **1984**, *25*, 273. (e) Cyanuric chloride: Venkataraman, K.; Wagle, D. R. *Ibid.* **1980**, *21*, 1893 and ref 3c. (f) Ketene trapping: Boeckman, R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. (g) Sulfonium carboxylate cyclization: Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 5218. For very recent examples of macrolactamizations in special cases, see: (h) Reference 22 and references therein. (i) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063, and references therein. (j) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *Ibid.* **1989**, *111*, 1157. (k) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2021.

(29) (a) Black, D. K.; Landor, S. R.; Patel, A. N.; Whiter, P. F. *J. Chem. Soc. C* **1967**, 2260. (b) Marvel, C. S.; Garrison, W. E. *J. Am. Chem. Soc.* **1959**, *81*, 4737. (c) Starks, C. M. *Ibid.* **1971**, *93*, 195. (d) Pattison, F. L. M.; Stothers, J. B.; Woolford, R. G. *Ibid.* **1956**, *78*, 2253. (e) Hunsdiecker, H.; Hunsdiecker, C. *Chem. Ber.* **1942**, *75*, 294. (f) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947. (g) Baudart, P. *Bull Soc. Chim. Fr.* **1946**, 85. (h) Crombie, L.; Jacklin, A. G. *J. Chem. Soc.* **1957**, 1622. (i) Brown, H. C.; Georgegan, P. J. *Ibid.* **1970**, *35*, 1844. (j) Landini, D.; Rolla, F. *J. Org. Chem.* **1980**, *45*, 3527. (k) McGhie, J. F.; Ross, W. A.; Laney, D. H. *J. Chem. Soc.* **1962**, 2578. (l) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875.

[lit.[4] bp 158–163 °C (21 mmHg); lit.[29h] bp 124–126 °C (0.05 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 1.1–2.1 (m, 12 H), 2.34 (t, J = 7.6, 2 H), 4.9–5.9 (m, spin system as in 11-bromo-1-undecene, 3 H), 11.3 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 28.5, 28.6, 28.7, 28.8, 33.5, 33.9, 114.2, 139.1, 180.9; IR (film) 3500–2600, 1710 (s), 1640 (w) cm^{-1}.

9-Hydroxydecanoic Acid (1a). Prepared according to ref 29i: To a stirred solution of $Hg(OAc)_2$ (1.2 g, 3.7 mmol) in water (3 mL) was added first THF (3 mL) and then a solution of **5** (500 mg, 2.94 mmol) in THF (3 mL). Stirring was maintained at rt for 1 h. The final solution was treated cold (ice bath) with 3 M NaOH (3 mL) and $NaBH_4$ (3 mL of 0.5 M solution in 3 M NaOH) for 3 h at rt. Acidification with 1 M HCl, extraction with Et_2O, drying of the etherial extracts, evaporation of the solvent, and removal of traces of AcOH with anhydrous benzene in vacuo afforded 465 mg (84%) of a colorless oil (a solid below 0 °C) whose ^{1}H and ^{13}C NMR spectra were exactly coincident with those reported in ref 3c.

9-Bromodecanoic Acid (1b). Prepared according to ref 29j: **5** (460 mg, 2.70 mmol), methyltrioctylammonium chloride (100 mg, 0.24 mmol), and 48% HBr (2 mL, ca. 17 mmol) were stirred at 110 °C for 45 min. CH_2Cl_2 and 2 M HCl were added, the two phases were separated, and the aqueous one was extracted with more CH_2Cl_2. The combined organic layers were dried and evaporated, and the residue was purified by column chromatography (98:2 CH_2Cl_2/MeOH) to give 610 mg (90%) of **1b**: oil; bp 100 °C (0.075 mmHg) [lit.[3a] bp 80–95 °C (0.05 mmHg)]; ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 12 H), 1.70 (d, J = 6.6, 3 H), 2.35 (t, J = 7.3, 2 H), 4.12 (m, 1 H), 10.7 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.4, 27.6, 28.6, 28.8, 28.9, 34.0, 41.0, 51.8, 180.4; IR (film) 3400–2600, 1715 cm^{-1}.

9-Azidodecanoic Acid (1d). A solution of **1b** (1.6 g, 6.3 mmol), $Bu_4N^+Br^-$ (195 mg, 0.6 mmol), and NaN_3 (1.98 g, 30 mmol) in water (10 mL) was stirred at 80 °C for 16 h. Acidification with 3 M HCl, extraction with CH_2Cl_2, drying of the organic extract, removal of the solvent under vacuum, and separation by column chromatography (98:2 CH_2Cl_2/MeOH) afforded 1.29 g (95%) of **1d**: oil; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.6, 3 H), 1.2–1.8 (m, 12 H), 2.35 (t, J = 7.5, 2 H), 3.41 (m, 1 H), 11.0 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.3, 24.4, 25.8, 28.7, 29.0, 29.0, 33.9, 36.0, 57.8, 180.3; IR (film) 2600–2600, 2100, 1710 cm^{-1}. Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.30; H, 8.99; N, 19.70. Found: C, 56.64; H, 9.23; N, 19.35.

9-Aminodecanoic Acid (1c). Compound **1d** (300 mg, 1.39 mmol) was treated with an excess of H_2 (1 atm) in MeOH (10 mL) in the presence of 5% Pd/C (20 mg) for 1 h. Filtration through Celite and evaporation of the solvent gave 260 mg (1.38 mmol, 99%) of **1c**: dec 197 °C (lit.[29k] dec 203 °C); ^{1}H NMR (CD_3OD) δ 1.0–1.8 (m, 12 H), 1.36 (d, J = 6.6, 3 H), 2.25 (t, J = 7.6, 2 H), 3.35 (m, 1 H); IR (KBr) 3600–2500, 1630 (w), 1580 (s), 1550 (s) cm^{-1}.

***S*-Phenyl 9-Hydroxydecanethioate (6).** To a stirred solution of **1a** (240 mg, 1.28 mmol) in benzene (10 mL) at rt was added 2,2′-dipyridyl disulfide (425 mg, 1.95 mmol) and Ph_3P (510 mg, 1.95 mmol). After 1 h, thiophenol (0.67 mL, 6.45 mmol) was added, and stirring was maintained for 3 h. The final mixture was directly separated by column chromatography (3:1 CH_2Cl_2/AcOEt) to give 310 mg (86%) of **6**: oil; bp 195 °C (0.0075 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 12 H), 1.16 (d, J = 6.2, 3 H), 2.64 (t, J = 7.2, 2 H), 3.74 (m, 1 H), 7.39 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 23.3, 25.4, 25.5, 28.7, 29.0, 29.2, 39.1, 43.5, 67.9, 127.7, 129.0, 129.1, 134.3, 197.4; IR ($CHCl_3$) 3600, 1705 cm^{-1}.

Tetrabutylammonium 9-Aminodecanoate (7). Prepared according to ref 24 (treatment of **1c** with an equivalent amount of $Bu_4N^+OH^-$ and removal of water by coevaporation with toluene under vacuum) and utilized in situ without further purification: oil; ^{1}H NMR ($CDCl_3$) δ 0.9–2.2 (m, 45 H), 2.6 (m, 1 H), 3.4 (m, 8 H); IR (film) 3500–2800, 1570 cm^{-1}.

***S*-2-Pyridyl 9-Azidodecanethioate (8).** A solution of **1d** (650 mg, 3.0 mmol) and Et_3N (0.5 mL, 3.6 mmol) in CH_2Cl_2 (15 mL) was added to a solution of *S*-2-pyridyl chlorothioformate (3.5 mmol), prepared as indicated in ref 29l, in toluene (20 mL) at 0 °C. Stirring was maintained for 1 h. After addition of CH_2Cl_2, the mixture was washed with aqueous $NaHCO_3$, 1 M HCl, and aqueous NaCl. Drying of the organic layer, removal of the organic solvents under vacuum, and purification of the residue by column chromatography (3:1 CH_2Cl_2/AcOEt) afforded 810 mg (90%) of **8**: oil; ^{1}H NMR ($CDCl_3$) δ 1.2–1.9 (m, 12 H), 1.24 (d, J = 6.5, 3 H), 2.70 (t, J = 7.0, 2 H), 3.40 (m, 1 H), 7.32 (ddd, J = 7.4, 4.8, 1.2, 1 H), 7.62 (br d, J = 6.9, 1 H), 7.77 (td, J = 7.8, 1.9, 1 H), 8.65 (br d, J = 4.9, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4, 25.2 25.9, 28.7, 29.0, 29.0, 36.0, 44.1, 57.9, 123.4, 130.0, 137.0, 150.2, 151.4, 196.4; IR (film) 2100, 1710 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_4OS$: C, 58.82; H, 7.19; N, 18.29. Found: C, 58.70; H, 7.35; N, 17.98.

Pentachlorophenyl 9-Azidodecanoate (9). Prepared analogously to a method reported in ref 23: DCC (320 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added to **1d** (300 mg, 1.4 mmol) and pentachlorophenol (375 mg, 1.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After stirring for 2 h at 0 °C, the solution was filtered, the solvent was removed in vacuo, and the residue was separated by column chromatography (CH_2Cl_2) to give 375 mg (60%) of **9**: oil; ^{1}H NMR ($CDCl_3$) δ 1.1–1.9 (m, 12 H), 1.25 (d, J = 6.5, 3 H), 2.67 (t, J = 7.0, 2 H), 3.41 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4, 24.5, 25.9, 28.8, 29.0, 29.1, 33.5, 36.1, 57.9, 127.6, 131.3, 131.9, 144.1, 169.3; IR ($CHCl_3$) 2100, 1780 cm^{-1}.

Lactonizations. A solution of **1a** (188 mg, 1.0 mmol), 2,2′-dipyridyl disulfide (bis(2-pyridyl) disulfide) (330 mg, 1.5 mmol), and Ph_3P (420 mg, 1.6 mmol) in benzene (10 mL) was stirred for 1 h at rt (see entry 1 of Table I). After dilution with benzene (10 mL), the resulting solution was added, by means of a syringe pump (Sage), during 6 h, through a vertical cooler, to a flask containing a magnetically stirred solution of $AgClO_4$ (2.1 g, 10 mmol) in benzene (100 mL), immersed in a large thermostatic bath at 85 °C. Heating was maintained for 1 further h; the flask was then cooled externally. The solution was filtered, concentrated carefully in vacuo (ca. 20 mmHg), and separated by column chromatography (98:2 hexane/AcOEt) to afford 85 mg (50%) of pure **2** and then 42 mg (25%) of its cyclic dimer(s). Compound **2**:[3] oil; bp 60 °C (0.75 mmHg) [lit.[7a] bp 80 °C (9 mmHg); lit.[30] bp 60 °C (0.8 mmHg)]; R_f 0.40 (9:1 hexane/AcOEt), greenish blue spot by heating with phosphomolibdic acid; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 6.3, 3 H), 1.2–1.8 (m, 10 H), 2.0–2.5 (m, 4 H), 4.92 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.5, 20.7, 23.5, 24.1, 24.3, 27.1, 31.5, 35.2, 72.5, 173.7; IR ($CHCl_3$) 1720 cm^{-1}; MS m/z 170 (M^+). (The NMR and IR data are coincident with those reported in ref 7a.) Dimer(s) of **2**:[31] mp 64–67 °C; R_f 0.27 (hexane/AcOEt 9:1); ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 6.3, 2 × 3 H), 1.2–1.7 (m, 2 × 12 H), 2.30 (t, J = 6.6, 2 × 2 H), 4.94 (m, 2 × 1 H); ^{13}C NMR ($CDCl_3$) δ 20.0, 24.6, 24.8, 28.2, 28.9, 29.0, 34.4, 35.6, 70.4, 173.8; IR ($CHCl_3$) 1720 cm^{-1}; HRMS m/z 340.2617 (calcd for $C_{20}H_{36}O_4$, 340.2614).

The same procedure, but using 10 equiv of DMAP instead of 10 equiv of $AgClO_4$ (entry 2), did not give lactone **2** or its dimer; hydroxy thioester was mainly recovered. The result was the same in the absence of DMAP. In refluxing xylene, in the presence of 10 equiv of DMAP, mainly polymeric material was obtained (also see ref 7a and footnote 15 in ref 17).

Compound **1a** (188 mg, 1.0 mmol), bis(4-*tert*-butyl-1-isopropyl-2-imidazolyl)disulfide (595 mg, 1.5 mmol), Ph_3P (395 mg, 1.5 mmol), and toluene (10 mL) were stirred at 0 °C for 1 h (entry 3). The resulting solution was diluted with toluene, as in the previous text, and was maintained at 0 °C under Ar while it was slowly added, during 6 h, to benzene (100 mL) at 80 °C (thermostatic bath at 85 °C). Workup as in entry 1 afforded mainly starting material.[32] The same result was obtained in refluxing toluene.

The remaining lactonizations (entries 4–10) were carried out similarly, as pointed out in Table I. In entry 4, the cyclization flask contained 10 mmol of CF_3COOAg, 20 mmol of Na_2HPO_4, and 100 mL of benzene; a 5% yield of lactone and a 25% yield of its dimer were obtained after the previously mentioned usual workup; polymeric material was the principal product. In entry 5, 1 mmol of **1a** and 20 mmol of Et_3N in 20 mL of CH_3CN were slowly added, as always, to a solution of 10 mmol of 2-chloro-1-methylpyridinium iodide in 100 mL of CH_3CN at 80 °C.[33] In

(30) Kostova, K.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 1713.

(31) No efforts were done to separate the racemic mixture (*RR*, *SS*) from the meso isomer. Apparently, the sample was chromatographically and spectroscopically homogeneous.

(32) Nevertheless, the method works well with 15-hydroxypentadecanoic acid, since under our conditions we have obtained a 75% yield of the 16-membered lactone plus 5% of its dimer.

(33) The same procedure, when applied to 15-hydroxypentadecanoic acid, afforded a 44% yield of the 16-membered lactone and 11% of dimer.

entry 6, **1a** (188 mg, 1.0 mmol) was treated first with 2,4,6-trichlorobenzoic acid chloride (270 mg, 1.1 mmol) and Et_3N (112 mg, 1.1 mmol) in THF (10 mL) for 2 h at rt, and the solution was then filtered and diluted with benzene (up to 20 mL); the cyclization flask contained DMAP (1.22 g, 10 mmol) in benzene (100 mL) at 80 °C; regarding the workup, the final solution was washed with aqueous $NaHCO_3$ and then with 1 M HCl, before drying, evaporating, and separating the products by chromatography as above, to give 51 mg (30%) of **2** and 69 mg (40%) of dimer. In entry 7, **1a** (188 mg, 1.0 mmol) in 1,2-dichloroethane (20 mL) was added during 6 h to a mixture of DMAP (1.22 g, 10 mmol), DMAP-TFA (2.36 g, 10 mmol), and DCC (2.06 g, 10 mmol) in 1,2-dichloroethane (100 mL) at 80 °C in the presence of 4-Å MS; regarding the workup, 30 mL of MeOH and 5 mL of AcOH were added at the end, and the mixture was then concentrated to ca. 50 mL, diluted with Et_2O, filtered through Celite, evaporated, and separated by column chromatography in the usual way; apart from small amounts of lactones (see Table I), very polar byproducts, presumably including acylureas, were obtained (also see ref 12); starting material was not recovered. In entry 8, a solution of **1a** (188 mg, 1 mmol) and DEAD (1.6 mL, 10 mmol) in cold toluene was added in the usual way to Ph_3P (2.62 g, 10 mmol) in toluene (100 mL) at 80 °C, but only traces of lactones were detected; the reaction was repeated but with only 1.5 equiv of DEAD, with identical results, as well as with 1.5 equiv of DEAD and 1.5 equiv of Ph_3P at rt for 48 h, also without success, since only a 10% yield of dimer was obtained in addition to polymeric material. In entry 9, 1 mmol of **1a** in 20 mL of toluene was added to 100 mL of benzene at 80 °C containing 10 mmol of 3,3'-(chlorophosphoryl)bis(1,3-oxazolidin-2-one), also called *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), and 20 mmol of Et_3N; the standard workup was then followed. In entry, 10, the cyclization flask contained 10 mmol of Bu_2SnO and an excess of 4-Å MS; concerning the workup, 250 mL of cold water were added to the final mixture, the solution was extracted several times with hexane, and the combined organic layers were washed with water, dried, and evaporated; no lactone was detected in the reaction crude; the same result was obtained when only 1 equiv of Bu_2SnO (instead of 10 equiv) was utilized.

In entry 11, compound **1b** (250 mg, 1 mmol) in DMF (20 mL) was added in the usual way to Cs_2CO_3 (3.26 g, 10 mmol) in DMF (100 mL) at 80 °C. After addition of an excess of cold water and extraction with hexane, followed by standard column chromatography, a 40% yield of **2** and a 5% yield of dimer were obtained; unsaturated carboxylic acids were also isolated. In entry 12, the cyclization flask contained 10 mmol of K_2CO_3 in 100 mL of DMSO; at the end, an excess of cold water was added and the organic material was extracted several times with hexane; the standard workup afforded a 55% yield of **2** and a 20% yield of dimer.

Lactamizations. To a solution of mesitylenesulfonyl chloride (2.20 g, 10 mmol) and ethyldiisopropylamine (1.7 mL, 10 mmol) in benzene (100 mL), heated at 80 °C (see entry 17 of Table I), was added via a syringe pump as in the previous text, during 6 h, a solution of **7** (430 mg, 1 mmol) in a benzene/CH_2Cl_2 mixture (20 mL). After 1 further h at this temperature, the solvent was evaporated in vacuo and the residue was separated by column chromatography (98:2 and then 95:5 CH_2Cl_2/MeOH) to afford 17 mg (10%) of pure **3** and 42 mg (25%) of its cyclic dimer(s), as white solids. Compound **3**: mp 223–225 °C; R_f 0.23 (CH_2Cl_2/MeOH (95:5)), violet spot with Cl_2/*o*-tolidine;[34] ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 6.7, 3 H), 1.1–2.4 (m, 14 H), 4.03 (m, 1 H), 5.48 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 24.6, 25.1, 27.5, 28.1, 28.3, 36.2, 36.3, 44.5, 172.8; IR (KBr) 3270, 1635 cm^{-1}; HRMS m/z 169.1468 (calcd for $C_{10}H_{19}NO$, 169.1466). Dimer(s) of **3**:[31] mp 197–202 °C; R_f 0.17 (95:5 $CHCl_2$/MeOH); ^1H NMR ($CDCl_3$) δ 1.12 (d, J = 6.7, 2 × 3 H), 1.1–2.4 (m, 2 × 14 H), 4.05 (m, 2 × 1 H), 5.40 (br s, 2 × 1 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.8, 25.1, 27.5, 28.3, 28.6, 35.9, 36.1, 44.8, 173.0; IR (KBr) 3270, 1635 cm^{-1}; HRMS m/z 338.2932 (calcd for $C_{20}H_{38}N_2O_2$, 338.2933). The same result was obtained by using DMAP instead of $EtPr^i_2N$. When the trifluoroacetate of **1c** (1 mmol in ca. 20 mL of toluene) was treated with 1.2 mmol of $MesSO_2Cl$ and 1.2 mmol of $EtPr^i_2N$ for 2 h at rt and the resulting solution added during 6 h to 10 mmol of $EtPr^i_2N$ in 100 mL of toluene at 80 °C no lactam but polyamide was detected.[35]

In entry 18, we have repeated an earlier experiment from our lab by adding 1 mmol of **8** in 20 mL of benzene to a mixture of 10 mmol of $SnCl_2$, 40 mmol of 2-thiopyridone, and 40 mmol of Et_3N in 100 mL of CH_3CN at 80 °C, i.e., under the concentration conditions used all over this work. After 1 further h at this temperature, the solvent was removed in vacuo and the residue was treated with a 1:1 mixture of CH_2Cl_2 and MeOH and was filtered. A few drops of 30% H_2O_2 were added to the solution. One hour later on, the solvent was evaporated and the residue separated by column chromatography (CH_2Cl_2, then 98:2 CH_2Cl_2/MeOH, and finally 95:5 CH_2Cl_2/MeOH) to afford a 20% yield of **3** and a 25% yield of its dimer;[36] ca. 10% of the starting azide **8** was recovered.

A solution of **8** (306 mg, 1.0 mmol) in CH_3CN (20 mL) was added during 6 h to a flask containing a magnetically stirred solution of freshly prepared benzeneselenol[37] (2.1 mL, 20 mmol) and Et_3N (2.8 mL, 20 mmol) in anhydrous CH_3CN (100 mL) at 80 °C (see entry 19). After heating for 1 further h, a stream of air was passed through the solution for 10 min, the solvent was removed in vacuo, and the residue was filtered through a pad of SiO_2 (first with CH_2Cl_2, to separate PhSeSePh, and then with 90:10 CH_2Cl_2/MeOH). The last fraction was concentrated and treated for 1 h with a few drops of 30% H_2O_2. Evaporation in vacuo and separation of the residue by column chromatography, with 98:2 CH_2Cl_2/MeOH and then 95:5 CH_2Cl_2/MeOH as the eluents, gave 50 mg (30%) of **3** and 67 mg (40%) of cyclic dimer(s).

A solution of **8** (306 mg, 1.0 mmol) in CH_3CN (20 mL) was added during 6 h to a flask containing anhydrous $SnCl_2$ (1.90 g, 10 mmol), freshly prepared benzeneselenol (3.20 mL, 30 mmol), Et_3N (4.20 mL, 30 mmol), and anhydrous CH_3CN (100 mL) (see entry 20). Working as in the previous example, 76 mg (45%) of **3** and then 42 mg (25%) of dimer were isolated. The same result was obtained when DMAP was utilized instead of Et_3N. In entry 21 the procedure was the same than in entry 20, except that the treatment with H_2O_2 was not required.

The remaining lactamizations were attempted under identical concentration conditions, as indicated in Table I. In entry 13, a suspension of 1 mmol of **1c** in xylene was added during 6 h (peristaltic pump) to 10 mmol of Bu_2SnO in 100 mL of xylene(s) maintained at 80 °C, in the presence of 4-Å MS; when Bu_2SnO was used in catalytic amounts, the same result was obtained; moreover, by heating at reflux instead of at 80 °C in the same solvent—mixture of xylene isomers—only traces of lactams were detected. In entry 14, 1 mmol of **1c** was treated with 2 mmol of diphenyl phosphorazidate ($(PhO)_2PON_3$, DPPA) and 1 mmol of Et_3N in 5 mL of DMF for 1 h, and then the mixture was diluted with more DMF and added in the usual way to 10 mmol of DMAP in 100 mL of DMF at 80 °C; no lactam was detected (Cl_2/*o*-tolidine test on TLC)[34] in the final mixture or after removal of the solvent in vacuo, addition of CH_2Cl_2, washing with 2 M HCl, drying, and evaporation; the trifluoroacetate of **1c** was also submitted to identical conditions with the same result.[38] In entry 15, the trifluoroacetate of **1c** (1 mmol in 20 mL of DMF) was added in the usual way to a flask containing 10 mmol of Ox_2POCl and 20 mmol of Et_3N in 100 mL of toluene; only very polar products were detected; in another experiment, **1c** was treated directly with Ox_2POCl under conditions very similar to those reported in ref 22 (ca. 6×10^{-3} M toluene solution, 4 equiv of Ox_2POCl, 10 equiv of $EtPr^i_2N$, 80 °C, 18 h, 4-Å MS); only traces of lactam and dilactam were observed. In entry 16, to a suspension of 1.0 mmol of the hydrochloride of **1c** in 10 mL of CH_2Cl_2 was added 1.2 mmol of DCC in 5 mL of CH_2Cl_2 and 1.2 mmol of pentachlorophenol

(34) Reindel, F.; Hoppe, W. *Chem. Ber.* **1954**, *87*, 1103.

(35) We carried out this additional experiment to evaluate whether the excess of $MesSO_2Cl$ (10 mmol under our conditions) could be detrimental or not, since the amine groups, apart from attacking on the mixed anhydride just formed, could partially react with the remaining mesitylenesulfonyl chloride.

(36) We had earlier obtained better yields of lactams using a 1:15:60:60 ratio of 8/$SnCl_2$/2-thiopyridone/Et_3N instead of the present 1:10:40:40 ratio (see ref 25).

(37) Reich, H. J.; Cohen, M. L. *J. Org. Chem.* **1979**, *44*, 3148.

(38) Possible shortcomings of the method, due to the disproportionation of the mixed anhydride in heating, had been earlier pointed out in footnote 15 of ref 21.

in 5 mL of CH_2Cl_2; after stirring for 12 h at rt, the solution was filtered, the filtrate was evaporated, and the residue was dissolved in 10 mL of DMF and added in the usual way to 100 mL of pyridine at 80 °C; after removal of the solvent in vacuo, the residue contained only traces of lactams.

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Registry No. **1a**, 40151-97-1; **1b**, 134781-66-1; **1c**, 134781-68-3; **1d**, 134781-67-2; **2**, 65371-24-6; **2** dimer (isomer 1), 134876-80-5; **2** dimer (isomer 2), 134876-82-7; **3**, 134781-56-9; **3** dimer (isomer 1), 134876-81-6; **3** dimer (isomer 2), 134876-83-8; **4**, 112-43-6; **5**, 14436-32-9; **6**, 134781-57-0; **7**, 134781-59-2; **8**, 134781-60-5; **9**, 134781-61-6; **10**, 134781-62-7; **11**, 134781-63-8; **12**, 106262-52-6; **13**, 134781-64-9; **14**, 76691-55-9; methyl 10-bromodecanoate, 134781-65-0; methyl 9-decenoate, 25601-41-6; pentachlorophenol, 87-86-5; *S*-2-pyridyl chlorothioformate, 73371-99-0; 11-bromo-1-undecene, 7766-50-9; 10-bromodecanoic acid, 50530-12-6.

Supplementary Material Available: Data for **10-14**; ^1H and ^{13}C NMR spectra of **6**, **9**, **11**, **12**, and **14** (11 pages). Ordering information is given on any current masthead page.

Synthesis of Alkynylcyclooctatetraenes and Alkynylcubanes

Philip E. Eaton* and Daniel Stössel

Department of Chemistry, The University of Chicago, Chicago, Illinois 60637

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The couplings of a variety iodocubanes with terminal acetylenes in refluxing NEt_3 in the presence of Cu(I) and Pd(0) were examined. The products, isolated in about 50% yield, were not alkynylcubanes but were instead the first examples of alkynyl-1,3,5,7-cyclooctatetraenes. The first examples of alkynylcubanes (cubylacetylenes) were themselves synthesized in modest yield by Negishi's procedure from alkyl cubyl ketones. Cubylacetylenes were shown to be stable under Heck-like coupling conditions and potentially useful thereby for the introduction of the cubylacetylene moiety into complex systems.

The discovery that ortho-metalation technology could be modified to apply to appropriately activated strained systems has made it possible to prepare a wide variety of substituted cubanes.[1] In this paper, with the same goal still in mind, we consider a different approach: transition metal catalyzed coupling reactions of halocubanes[2] with terminal acetylenes. The expected products, alkynylcubanes (cubylacetylenes), have not been reported previously; nothing is known of their chemistry.

The Heck reaction, in one or another of its forms, is a very useful method for carbon-carbon bond formation between unsaturated centers.[3] Sonogashira and Just and their co-workers have successfully adapted the method to the coupling of iodobenzene with terminal acetylenes.[4] This process is most efficient when both Cu(I) and Pd(II or 0) are present in catalytic amounts. The reactions probably proceed by palladium insertion into the carbon-iodine bond, nucleophilic displacement of a palladium ligand by a copper acetylide, and finally coupling with extrusion of palladium.[4a] Normally, saturated alkyl iodides are unsuitable participants as ionization and/or β-elimination reactions open pathways more-than-competitive with the desired coupling.

Although cubane is, representationally, a saturated hydrocarbon, there being four bonds to each carbon, the high percentage of s character in the cubane carbon exocyclic orbital implies a certain vinyl-like character in substituent bonding.[5] Ionization of cubyl halides, although possible,[6] is exceedingly difficult, and β-elimination to cubene (1,2-dehydrocubane), again although possible,[7] is a high-energy process unlikely under Heck reaction conditions. These substantial differences between cubyl halides and typical saturated halides encouraged us to attempt Heck coupling of cubyl halides with terminal acetylenes.

Application of the optimum conditions reported[8] for coupling of iodobenzene with terminal acetylenes (2 mol % $Pd(PPh_3)_4$, 3 mol % Cu_2Br_2, triethylamine, room temperature, excess of the acetylene) was ineffective when applied to a variety of iodocubanes. No coupling was observed with 1-hexyne or with phenylacetylene even after a 24 h reaction time; the starting iodides were recovered in good yield (80-90%). However, when the temperature was raised to near 90 °C (refluxing triethylamine), coupling reactions did occur, but did not give cubane-containing products. Instead, the reactions of substrates **1-5** with 1-hexyne or with phenylacetylene gave alkynyl-1,3,5,7-cyclooctatetraenes (**6-10**).[9] Relatively large amounts of metal catalysts were required [16 mol % Pd(0) and 24 mol % Cu(I)] for the conversion to be complete within 5 h. The reaction appears to be general with respect to both the iodocubane and the acetylene; about 50% isolated yields of alkynylcyclooctatetraenes were obtained no matter the variation in substrate or acetylene.

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(8) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453.

(9) Dimers of the starting acetylene (a 2- to 4-fold excess was usually used) were also isolated. Cu(I) salts are known to promote the dimerization of acetylenes. See: Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; Chapter 9.

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