heating at reflux for 48 h. The mixture was cooled, and the solvent was evaporated. The residue was suspended in water and extracted with chloroform (3 × 100 mL). Removal of solvent furnished 0.102 g of pyridone **17** (43%) recrystallized from 95% EtOH: mp 228 °C; IR ($CHCl_3$) ν 3280, 3180, 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 1.71 (m, 4 H), 2.11 (s, 3 H), 2.44 (m, 2 H), 2.63 (m, 2 H), 4.41 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.3, 16.7, 21.4, 22.7, 24.1, 27.3, 61.2, 114.1, 144.1, 150.6, 161.1, 167.3; UV (EtOH) λ_{max} 230 (ϵ 5506), 316 nm (ϵ 9471); mass spectrum, m/e (relative intensity) 235 (46), 190 (59), 189 (36), 163 (100), 162 (22), 161 (60), 134 (16), 133 (59); high resolution, m/e calcd for $C_{13}H_{17}NO_3$ 235.1208, found, 235.1202.

10-Methyl-1,2,3,4,7,8,9,10-octahydro-6(5*H*)-phenanthridinone (18). Condensation of vinyl isocyanate **1** from 0.126 g (1 mmol) of cyclohexenecarboxylic acid (via procedure A) and 0.155 g (1 mmol) of enamine **15** produced 52% of pyridone **10** as a white solid after recrystallization from 95% EtOH: mp 248–250 °C; UV (CH_3OH) λ_{max} 234 (ϵ 3326), 305 nm (ϵ 5090); IR ($CDCl_3$) ν 3300, 2900, 2850, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6 Hz, 3 H), 1.60–1.86 (m, 8 H), 2.30–2.90 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 16.3, 20.2, 21.8, 22.9, 23.9, 27.2, 28.5, 29.1, 112.9, 123.2, 138.0, 153.5, 163.5; mass spectrum, m/e (relative intensity) 217 (100), 216 (40), 203 (15), 202 (80), 192 (18), 97 (50), 96 (15), 83 (20), 81 (16), 69 (30), 57 (40), 55 (55), 43 (50), 41 (55), 39 (15), 29 (15), 27 (15); high resolution, m/e calcd for $C_{14}H_{19}NO$ 217.1466, found 217.1467.

6,7,8,9,10,11-Hexahydro-5*H*-benzo[*h*]cyclopent[*c*]isoquinolin-5-one (21). Condensation of the isocyanate derived via procedure A from 1.12 g (10 mmol) of cyclopentenecarboxylic acid with 1.99 g (10 mmol) of enamine **19** gave 1.35 g (57%) of pyridone **21** (95% EtOH): mp 289–292 °C; IR ($CHCl_3$) ν 3240, 3130, 3010, 2410, 2860, 1635, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (m, 2 H), 2.70 (m, 2 H), 2.81 (m, 4 H), 3.07 (t, J = 6 Hz, 2 H), 7.34 (m, 4 H), 8.82 (d, J = 9 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 21.7, 25.7, 27.1, 27.9, 30.7, 116.7, 125.7, 125.9, 126.8, 132.5, 135.3, 147.6, 161.1; UV (EtOH) λ_{max} 262 (ϵ 5275), 268 (ϵ 5038), 350 nm (ϵ 11 499); mass spectrum, m/e (relative intensity) 237 (100), 236 (28), 218 (4), 208 (9). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.74; H, 6.34; N, 6.05.

7,8,9,10,11,12-Hexahydrobenzo[*i*]phenanthridin-5(6*H*)-one (22). Reaction of isocyanate **1** derived from 1.26 g (10 mmol) of cyclohexenecarboxylic acid via procedure A with 1.99 g (10 mmol) of enamine **19** gave 1.53 g (61%) of pyridone **22** (95% EtOH): mp >300 °C; IR ($CHCl_3$) 3370, 3250, 3130, 2920, 1640, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–2.00 (m, 4 H), 2.50–2.88 (m, 8 H), 7.10–7.22 (m, 4 H); ^{13}C NMR (CD_3OD) δ 20.9, 22.2, 23.4, 23.9, 26.5, 27.1, 110.9, 119.2, 125.6, 126.1, 126.5, 132.3, 135.5, 141.5, 150.1, 160.0; UV (EtOH) λ_{max} 240 (ϵ 9414), 248 (ϵ 8577), 344 nm (ϵ 2071); mass spectrum, m/e (relative intensity) 251 (100), 250 (22), 223 (13), 22 (14). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.81; N, 5.57. Found: C, 80.91; H, 6.60; N, 5.60.

10-Methoxy-1,2,3,4,7,8-hexahydrobenzo[*k*]phenanthridin-6(5*H*)-one (23). Reaction of the vinyl isocyanate prepared from 0.25 g (2 mmol) of cyclohexenecarboxylic acid (via procedure A) and 0.455 g (2 mmol) of enamine **20** gave 0.25 g (46%) of pyridone **23** (95% EtOH): mp 292–93 °C; IR (KBr) ν 3400, 1635, 1440, 1320, 1250, 1225, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (m, 2 H), 1.71 (m, 2 H), 2.73–2.81 (m, 8 H), 3.87 (s, 3 H), 6.79–6.86 (m, 2 H), 7.62 (d, J = 9 Hz, 1 H), 12.20 (m, 1 H); ^{13}C NMR ($DCCl_3$) δ 21.6, 21.7, 23.7, 27.3, 28.6, 29.6, 45.8, 55.2, 110.7, 112.3, 113.5, 124.2, 125.6, 129.6, 140.5, 142.9, 146.3, 159.6, 162.9; UV (EtOH) λ_{max} 234 nm (ϵ 19 865); mass spectrum, m/e (relative intensity) 298 (78), 280 (100), 279 (8), 266 (9). Anal. Calcd or $C_{18}H_{19}NO_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.53; H, 6.71; N, 4.50.

8,9,10-Trimethoxy-2,3,6,7-tetrahydro-1*H*-benzo[*f*]cyclopenta[*c*]quinolin-4(5*H*)-one (25). Reaction of the vinyl isocyanate derived from 0.422 g (1.6 mmol) of 3,4-dihydro-5,6,7-trimethoxy-2-naphthoic acid via procedure A and 1 equiv of 1-pyrrolidino-1-cyclopentene yielded 0.177 g (34%) of pyridone **25** (95% EtOH): mp 279–281 °C; IR (Nujol) ν 3200–2800, 1655, 1600, 1472, 1417, 1368, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (m, 2 H), 2.95 (m, 6 H), 3.25 (t, J = 7 Hz, 2 H), 2.89 (s, 3 H), 3.91 (s, 3 H), 3.93 (s, 3 H), 6.96 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.4, 24.5, 26.3, 29.6, 36.0, 56.4, 60.9, 61.0, 105.8, 111.3, 120.90, 129.2, 130.8, 140.4, 144.5, 150.5, 151.8, 152.6, 160.5; mass spectrum, m/e (relative intensity) 327 (24), 312 (24), 183 (18), 165 (18), 156 (16), 155 (37), 153 (12). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.27. Found: C, 69.66; H, 6.60; N, 4.08.

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Organometallic Ring-Opening Reactions of *N*-Acyl and *N*-Alkoxycarbonyl Lactams. Synthesis of Cyclic Imines

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The reactions of hexyl- and phenylmagnesium bromides with *N*-acyl and *N*-alkoxycarbonyl lactams in tetrahydrofuran at −78 °C have been performed to determine the factors affecting the regioselectivity. *N*-Pivaloyl γ- and δ-lactams undergo the ring-opening reactions with both Grignard reagents, whereas on the *N*-benzoyl γ-lactam a complete selectivity is achieved only with phenylmagnesium bromide. The *N*-Cbz γ- and δ-lactams preferentially react at the exocyclic carbonyl group, especially with hexylmagnesium bromide. The *N*-Boc five- to eight-membered lactams undergo the ring-opening reaction to give *N*-Boc-ω-amino ketones, although the efficiency slightly decreases by increasing the ring size. The deprotection of the *N*-Boc-ω-amino ketones with trifluoroacetic acid easily affords the corresponding five- to seven-membered cyclic imines. Pyridine alkaloids containing the cyclic imine moiety have been prepared by a modified route, exploiting the more easily available pyridyllithium reagents, instead of the corresponding Grignard reagents.

The selective ring-opening reaction of *N*-methyl lactams **1** ($n \geq 1$; R′ = CH_3) to give ω-methylamino ketones **2** by means of organometallic reagents cannot be generally accomplished. In fact, forcing experimental conditions are required owing to the low reactivity of the carbonyl group, so that mixtures of several products are obtained, depending on the ring size of the lactam and the nature of the organometallic reagent.[1-3] Only when aryl organo-

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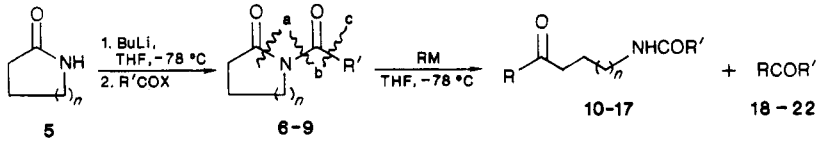
Table I

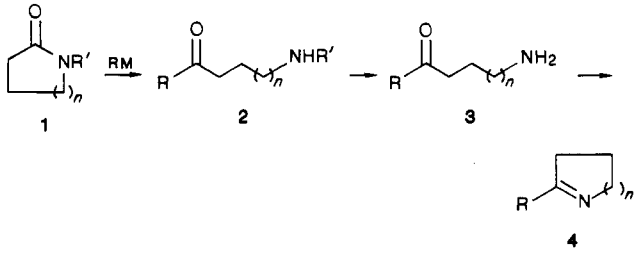


5 6-9 10-17 18-22

	n	R'COX	(yield, %)[a]	RM	(yield, %)[a]	(yield, %)[a]
5a	1	*t*-BuCOCl	**6a** (85)	*n*-C_6H_{13}MgBr	**10a** (85)	–
5a	1	*t*-BuCOCl	**6a** (–)	*n*-C_6H_{13}MgBr	**10a** (82)[b]	–
5b	2	*t*-BuCOCl	**6b** (–)	*n*-C_6H_{13}MgBr	**10b** (97)[b,c]	–
5a	1	PhCOCl	**7** (88)	*n*-C_6H_{13}MgBr	**11** (77)	**18** (12)
–	–	–	**7** (–)	PhMgBr	**12** (85)	–
5a	1	$PhCH_2OCOCl$	**8a** (82)	*n*-C_6H_{13}MgBr	**13a** (22)	**19** (43)
5b	2	$PhCH_2OCOCl$	**8b** (80)	*n*-C_6H_{13}MgBr	**13b** (5)	**19** (72)
–	–	–	**8a**	PhMgBr	**14a** (70)	**20** (17)
–	–	–	**8b**	PhMgBr	**14b** (30)	**20** (48)
–	–	–	**8b**	*n*-BuLi	**15** (17)	**21**[d] (35)
5a	1	$(t\text{-BuOCO})_2O$	**9a** (86)	*n*-C_6H_{13}MgBr	**16a** (85)	–
5b	2	$(t\text{-BuOCO})_2O$	**9b** (80)	*n*-C_6H_{13}MgBr	**16b** (70)	–[e]
5c	3	$(t\text{-BuOCO})_2O$	**9c** (75)	*n*-C_6H_{13}MgBr	**16c** (60)	–[e]
5d	4	$(t\text{-BuOCO})_2O$	**9d** (76)	*n*-C_6H_{13}MgBr	**16d** (57)	**22**[e] (6)
–	–	–	**9a**	PhMgBr	**17a** (85)	–
–	–	–	**9b**	PhMgBr	**17b** (75)	–[e]

[a] Yield of pure compounds, after flash chromatography. [b] Yield based on **5**, since **6** was prepared in situ. [c] Yield of crude product (95% pure). [d] Benzyl alcohol (8% yield) was also obtained. [e] A byproduct (**26** or **27**, Scheme II) was isolated.

Scheme I



metallic reagents are used are the compounds **2** selectively obtained from δ- or larger lactams.[2,3] *N*-Vinyl lactams **1** (n = 1, 3, R' = $CH{=}CH_2$) more easily react with organolithium reagents to afford, after acidic hydrolysis, the cyclic imines **4**,[4,5] through the intermediates **2** and **3** (Scheme I).

We looked for a new general method allowing the easy preparation of N-substituted ω-amino ketones, and of cyclic imines from them, starting from N-unsubstituted lactams and making use of the common Grignard reagents. We envisioned *N*-acyl and *N*-alkoxycarbonyl lactams **6–9** as key intermediates,[6] possibly formed in situ in the synthetic sequence, provided that they are able to undergo a selective attack on the endocyclic (ring) carbonyl group to give **10–17** (Table I).

At the beginning of our work, we could not find literature examples of organometallic reactions on *N*-acyl lactams or unsymmetrical imides. More recently, however, selective reactions of an indolyllithium reagent on 1-benzoyl-2-pyrrolidinone[7] and of Grignard reagents on *N*-Cbz and *N*-Boc proline derivatives[8] have been reported, although a thorough study on the factors governing the regioselectivity has not been undertaken. Much more information is instead available about the reactions of nucleophiles (hydride, hydroxide, and alkoxide ions, amines) on *N*-acyl[9] and *N*-alkoxycarbonyl lactams,[10] as well as on the structurally related *N*-Boc amides,[11] and *N*-acyl[12] and *N*-(alkoxycarbonyl)-1,3-oxazolidin-2-ones.[13] These reports show that the nucleophilic attack can occur on both the carbonyl groups of the unsymmetrical substrates, depending on the reaction conditions (kinetic or thermodynamic control), the nature of the nucleophile, the relative steric hindrance around the carbonyls, and other possible factors.

In this paper we present a preliminary study on the regioselectivity pattern of the organometallic addition to the activated lactams **6–9**. We also describe the easy and rapid synthesis of 2-substituted cyclic imines from lactams by a sequence that involves the in situ introduction of the

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N-Boc group, the organometallic ring-opening reaction, and the nitrogen deprotection with concomitant ring-closure and dehydration.

Results and Discussion

The *N*-pivaloyl, *N*-benzoyl, *N*-Cbz, and *N*-Boc lactams **6–9** (Table I) were prepared by metalation of the lactams **5** with butyllithium (BuLi) in tetrahydrofuran (THF) at −78 °C, followed by the addition of an equivalent amount of the appropriate acylating reagent. The optimum experimental conditions to perform the Grignard reaction were determined by working on the *N*-pivaloyl γ-lactam (**6a**) and then applied to all the intermediates (**6–9**).

When a slight excess of hexylmagnesium bromide was added to **6a** in THF at −78 °C, the product **10a** was cleanly obtained through the ring-opening reaction (path a), the main impurity being unreacted **6a**. We want to stress here that it is possible and convenient to carry out in the same flask the two-step sequence (from **5** to **10**) avoiding isolation of **6**: by this quick procedure both **10a** and **10b** were obtained in high yield.

On 1-benzoyl-2-pyrrolidinone (**7**) the reactions with hexyl- and phenylmagnesium bromide were performed, and in both cases, good yields of the desired products **11** and **12** were obtained, but the two reactions exhibited different degrees of regioselectivity. In fact, a discrete amount of 1-phenyl-1-heptanone (**18**) was produced in the former reaction (path b), whereas only traces of the corresponding product, benzophenone, could be revealed by TLC and GC analyses of the latter reaction mixture.

The dependence of the regioselectivity on the nature of the organometallic reagent and on the ring size of the lactam could be more clearly evinced by the results obtained from the *N*-Cbz lactams **8**, which reacted preferentially through path b, since benzyl heptanoate (**19**) was prevalent with respect to the *N*-Cbz-ω-amino ketones **13a,b**, especially from the δ-lactam.

Shifting from hexyl- to phenylmagnesium bromide, we observed that the attack to the ring carbonyl group was facilitated, as on the *N*-benzoyl lactam **7**: **14a** was the main product, more than 4 times as abundant as benzyl benzoate (**20**), although the yield of the homologous **14b** was again inferior to that of **20**.

By substitution of butyllithium for the Grignard reagent, the products **15** and **21** were formed in about the same ratio as **13a**/**19**, although in lower yields, and were accompanied by benzyl alcohol (8% yield), produced through path c. Only traces of benzyl alcohol were instead revealed by GC analysis of some Grignard reaction mixtures.

The *N*-Boc γ-lactam (**9a**) reacted cleanly with both hexyl- and phenylmagnesium bromide to yield, after quenching with 2 N HCl[14] and column chromatography, the *N*-Boc-γ-amino ketones **16a** and **17a** in good yield. The conversion of the homologous *N*-Boc lactams **9b–d** was less efficient, owing to the competitive α-metalation reaction, since discrete amounts of unreacted **9b–d** were evident by TLC analysis. The yields of the desired products **16a–d** decreased by increasing the ring size. *tert*-Butyl heptanoate (**22**, path b) was isolated in 6% yield from the reaction of **9d** with hexylmagnesium bromide, but only in trace amounts (revealed by GC analysis) from **9c**. Furthermore we examined carefully the reaction mixtures of **9a,b** with phenylmagnesium bromide and ascertained the absence of *tert*-butyl benzoate as well as *N*-benzoyl lactams (path c). It was so demonstrated that the *N*-Boc lactams undergo the organometallic addition at the ring carbonyl far more selectively than the *N*-Cbz analogues, confirming the previous observation on the hydrolysis and alcoholysis of the same substrates[10a–c] as well as of oxazolidinones.[13]

A byproduct was, however, formed in the Grignard reactions of the *N*-Boc lactams **9b–d**, expecially from **9c**: in a separate experiment, in which the temperature was allowed to reach 0 °C, its amount increased at the expense of the main product. The byproducts isolated from each reaction mixture had spectroscopic properties consistent with the *N*-(ω-oxoalkyl) secondary amide structure (**26b–d** and **27b**) and were presumably produced through the reaction of the *N*-Boc magnesium salt (**25**) with the magnesium enolate of the starting lactam (**23**) (Scheme II).

The deprotection of the amine functionality was checked on the *N*-pivaloyl-, *N*-benzoyl-, and *N*-Boc-amino ketones, which could be obtained in fair to good yields by the previously described procedures. The hydrolysis of **11** could be accomplished under the conditions described for a similar benzamide[7] (KOH–H_2O–EtOH, 48 h at reflux), the pyrroline **30a** being obtained in 52% yield, but impure by TLC and GC analyses. The *N*-pivaloyl derivative **10b** was inert toward hydrolysis (LiOH and $Ba(OH)_2$ at reflux) and aminolysis (aqueous ammonia, and butylamine in refluxing toluene). Finally, the treatment of the *N*-Boc-ω-amino ketones **16** and **17** with trifluoroacetic acid (TFA), followed by sodium hydroxide, afforded the cyclic imines **30** and **31** in good yields (Table II). The crude bases showed satisfactory ^1H NMR spectra, but their IR spectra generally presented absorptions that we attributed to the corresponding ω-amino ketones and their ring tautomers.

Scheme II

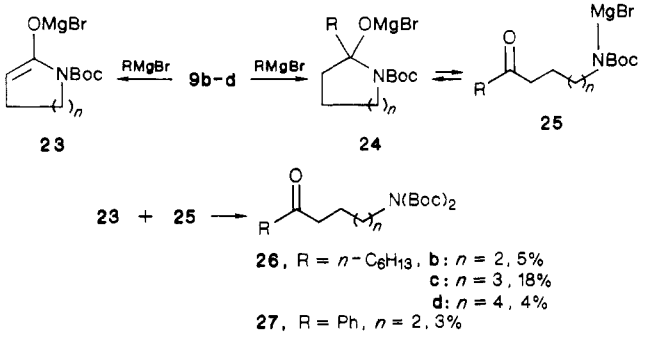
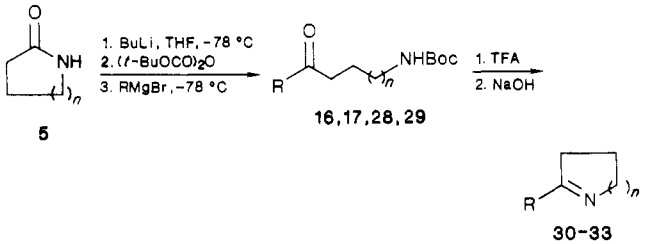


Table II

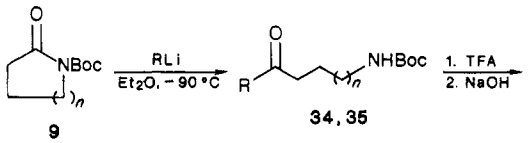


	n	R		(yield, %)
5a	1	*n*-C_6H_{13}	**16a**	**30a**, (77)[a] (60)[b]
5b	2	*n*-C_6H_{13}	**16b**	**30b** (74)[a]
5c	3	*n*-C_6H_{13}	**16c**	**30c** (70)[a,c]
5a	1	Ph	**17a**	**31a** (83)[a] (69)[b]
5b	2	Ph	**17b**	**31b** (71)[a]
5b	2	*n*-C_3H_7	**28**	**32** (44)[b]
5b	2	*n*-$C_{11}H_{23}$	**29**	**33** (48)[b]

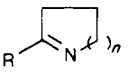
[a] Yield based on starting compound **16** or **17**. [b] Yield based on starting compound **5** (the *N*-Boc-ω-amino ketone was not purified). [c] Product obtained from **16c** + **26c** (Scheme II, see text).

(14) Quenching with saturated aqueous NH_4Cl afforded a more complex reaction mixture, probably containing the ring tautomer of the *N*-Boc-amino ketone and the corresponding cyclic enamine(s).

Table III



9 34, 35



36, 37

	n	R		(yield, %)[a]
9a	1	3-pyridinyl	**34a**	**36a** (40)
9b	2	3-pyridinyl	**34b**	**36b** (56)
9a	1	2-pyridinyl	**35**	**37** (63)

[a] Yield of pure compounds, after flash chromatography.

Column chromatography generally allowed us to obtain very pure imines, free also from the isomeric cyclic enamines, on the basis of the reported IR,[15] UV,[16] ^{1}H NMR,[17] and ^{13}C NMR[18] spectra. The yields appeared to decrease with increasing ring size, presumably for the correspondingly greater amounts of amino ketones in the crude reaction products. Only from **16d** the cyclic imine was not obtained: the crude reaction product was a mixture of polar compounds (TLC), probably containing 1-aminotridecan-7-one (IR, NMR), although we could not isolate it by column chromatography.

The formation of the secondary amides **26** and **27** gives no problem if the cyclic imines are the target of the synthetic sequence: in fact, **16c** and **26c**, separately treated with TFA–NaOH, gave the same crude base (**30c**). Hence, it being unnecessary to purify the reaction products coming from the Grignard reactions, a more expeditious route to the cyclic imines is possible starting from the lactams **5** by performing in the same flask the N-acylation and Grignard steps and submitting the crude isolated products to the TFA–NaOH treatment. By this protocol we prepared from **5a,b** the cyclic imines **30a**, **31a**, **32** (δ-coniceine), and **33** in satisfactory yields after a single final chromatographic purification (Table II).

1-Pyrrolines and 1-piperideines are useful intermediates, e.g., for the synthesis of indolizidine and quinolizidine alkaloids[19] and of the major ant venom components from the genera *Solenopsis* and *Monomorium*.[20] Furthermore, the cyclic imine moiety is a feature of some pyridine alkaloids: myosmine (**36a**), anabaseine (**36b**), and apoferrorosamine (**37**) (Table III). Since the pyridylmagnesium bromides required for their synthesis cannot be easily prepared,[21] we employed the corresponding lithium reagents, prepared by bromine–lithium exchange on 2- and 3-bromopyridine.[22] By the addition of the *N*-Boc lactam **9a** or **9b** to the pyridyllithium reagent in ether at −90 °C we obtained the crude products **34a,b** and **35**, which were converted to the alkaloids **36a,b** and **37**, respectively, by the TFA–NaOH treatment.

Conclusions

The regioselectivity of the organometallic addition to *N*-acyl and *N*-alkoxycarbonyl lactams is affected principally by the steric and electronic properties of the substituent on the exocyclic carbonyl group, by the nature of the organic radical R in the organometallic reagent RM (alkyl or aryl), and by the ring size of the lactam. From the results of the reaction on *N*-benzoyl and *N*-Cbz lactams it is inferred that the extent of attack to the ring carbonyl group decreases by increasing the ring size (from five- to six-membered rings) and shifting from phenyl- to hexylmagnesium bromide. The ring-opening reaction with both alkyl and aryl Grignard reagents is possible on the *N*-pivaloyl and *N*-Boc lactams. However, the removal of the N-substituent is easy only from the *N*-Boc-ω-amino ketones, allowing the synthesis of five- to seven-membered cyclic imines in satisfactory to good overall yields.

So far 2-substituted cyclic imines have been available by a variety of methods.[23] Some of them exploit lactams as starting materials, for example, the hydrolysis of differently N-substituted α-acyl lactams[24] and the rearrangement of *N*-acyl lactams by distillation over calcium oxide.[25] Our procedure can also be compared with several methods, by which the ring substituent is introduced by means of organometallic reagents, i.e.: Grignard compounds on ω-halo nitriles,[15,26] cyclopropyl nitriles,[27] and thiolactim ethers;[28] organolithium compounds on *N*-vinyl lactams[4] and lactim ethers;[29] organoalanes on cycloalkanone oxime tosylates.[30] Cycloalkane tertiary azides[31] and ω-azido ketones[32] are also advantageous precursors of cyclic imines.

Experimental Section

General. Spectral data were recorded on the following instruments: ^{1}H NMR, Varian EM390 (90 MHz, $CDCl_3$, TMS); ^{13}C NMR, Varian FT 80A ($CDCl_3$, TMS); IR, Perkin-Elmer PE 682; UV, Perkin-Elmer 402 (1-cm quartz cells); MS, double-focusing VG 7070E (70 eV). Melting points were determined on a Büchi 510 apparatus and are not corrected. Chromatographic

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separations were performed by using 70–230 mesh silica gel (flash chromatography) or 230–400 mesh silica gel (Merck). Capillary gas chromatography was performed on a Carlo Erba HRGC 5300 Mega Series apparatus, using an OV1 column (15 m, 0.1-μm film thickness). TLC analyses were carried out by using Merck plastic sheets coated with silica gel 60 F_{254} (layer thickness: 0.2 mm). Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under an argon atmosphere; diethyl ether was distilled over $LiAlH_4$ under argon. 2-Pyrrolidinone (**5a**), benzoyl chloride, and pivaloyl chloride were purchased from Merck and were distilled before use; BuLi (2.5 M solutions in hexane), 2-piperidinone (**5b**), and 1-azacyclooctan-2-one (**5d**) were obtained from Aldrich; ε-caprolactam (**5c**) was prepared via Beckmann rearrangement of cyclohexanone oxime; benzyl chloroformate and di-*tert*-butyl dicarbonate were available from Fluka. All the new compounds (**6b, 8a,b, 9c,d, 10a,b, 11, 13a,b, 14a,b, 15, 16a–d, 17a,b, 26b–d, 27, 30a–c**) had correct elemental analyses (C ± 0.3%, H ± 0.2%, N ± 0.25%). The known compounds, including **6a**,[25c] **7**,[7,25b] **9a,b**,[10a] **12**,[33] **18–22**, **31a**,[26,34] **31b**,[35] **32**,[15b,29b,36] **33**,[37] **36a**,[38] **36b**,[38b] and **37**,[4c,27,39] were identified by comparison with authentic specimens or by comparison of their physical and spectroscopic properties with the literature data.

General Procedure for the Preparation of *N*-Acyl and *N*-Alkoxycarbonyl Lactams. In a three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet, the lactam **5** (30 mmol) is dissolved in anhydrous THF (100 mL). The solution is cooled at −78 °C, causing the precipitation of the insoluble lactams, and then BuLi (30 mmol) is added dropwise with stirring. After 30 min, a solution of the acylating agent (R'COX in Table I, 30 mmol) in THF (30 mL) is added dropwise, and the reaction mixture is stirred at −78 °C for 2–3 h. The reaction is quenched with saturated aqueous NH_4Cl (40 mL), and the organic phase is extracted with ether (3 × 50 mL), dried (Na_2SO_4), and evaporated to leave the crude product, which is purified by flash chromatography, eluting with cyclohexane–ethyl acetate mixtures.

1-(2,2-Dimethylpropanoyl)-1-azacyclopentan-2-one (6a):[25c] IR (neat) 1740, 1680 cm^{-1}; ^1H NMR δ 1.33 (s, 9 H), 2.07 (m, 2 H), 2.6 (t, 2 H), 3.86 (t, 2 H); MS, *m/e* (relative intensity) 169 (M^+, 6), 57 (91), 86 (69), 85 (73), 41 (72), 56 (24), 112 (21), 69 (23), 98 (17).

1-Benzoyl-1-azacyclopentan-2-one (7): mp 90–91 °C (lit.[25b] mp 91 °C); IR (Nujol) 1740, 1660 cm^{-1}; ^1H NMR δ 2.1 (m, 2 H), 2.58 (t, 2 H), 3.98 (t, 2 H), 7.5 (m, 5 H); MS, *m/e* (relative intensity) 189 (M^+, 38), 105 (100), 77 (39), 51 (26), 106 (4), 84 (3).

1-(Benzyloxycarbonyl)-1-azacyclopentan-2-one (8a): mp 34–36 °C; IR (Nujol) 1785, 1750, 1720 cm^{-1}; ^1H NMR δ 1.82 (m, 2 H), 2.32 (t, 2 H), 3.68 (t, 2 H), 5.2 (s, 3 H), 7.3 (m, 5 H); MS, *m/e* (relative intensity) 219 (M^+, 38), 91 (100), 86 (78), 107 (63), 85 (52), 65 (14), 113 (10).

1-(Benzyloxycarbonyl)-1-azacyclohexan-2-one (8b): IR (neat) 1770, 1720 cm^{-1}; ^1H NMR δ 1.72 (m, 4 H), 2.42 (t, 2 H), 3.67 (t, 2 H), 5.22 (s, 2 H), 7.3 (m, 5 H); MS, *m/e* (relative intensity) 233 (M^+, 12), 91 (100), 99 (63), 100 (58), 108 (43), 79 (29), 77 (20), 98 (17).

1-(*tert*-Butoxycarbonyl)-1-azacyclopentan-2-one (9a):[10a] IR (neat) 1790, 1750, 1720 cm^{-1}; ^1H NMR δ 1.51 (s, 9 H), 2.0 (m, 2 H), 2.5 (t, 2 H), 3.68 (t, 2 H); MS, *m/e* (relative intensity) 185 (M^+), 130 (100), 112 (97), 86 (84), 57 (71), 41 (65), 69 (36), 56 (29), 84 (19), 98 (10).

1-(*tert*-Butoxycarbonyl)-1-azacyclohexan-2-one (9b):[10a] mp 33–35 °C; IR (Nujol) 1780, 1740 cm^{-1}; ^1H NMR δ 1.55 (s, 9 H), 1.82 (m, 4 H), 2.51 (t, 2 H), 3.69 (t, 2 H); MS, *m/e* (relative intensity) 199 (M^+), 57 (100), 144 (55), 100 (37), 41 (27), 126 (25), 98 (18), 99 (18), 55 (17), 82 (12).

1-(*tert*-Butoxycarbonyl)-1-azacycloheptan-2-one (9c): mp 35–37 °C; IR (Nujol) 1770, 1720 cm^{-1}; ^1H NMR δ 1.52 (s, 9 H), 1.6–1.9 (m, 6 H), 2.63 (t, 2 H), 3.79 (t, 2 H); MS, *m/e* (relative intensity) 213 (M^+, 3), 85 (100), 158 (99), 41 (96), 114 (66), 57 (61), 140 (46), 69 (32), 39 (28).

1-(*tert*-Butoxycarbonyl)-1-azacyclooctan-2-one (9d): mp 34–36 °C; IR (Nujol) 1770, 1720 cm^{-1}; ^1H NMR δ 1.52 (s, 9 H), 1.6–2.0 (m, 8 H), 2.6 (t, 2 H), 3.8 (t, 2 H); MS, *m/e* (relative intensiy) 227 (M^+, 4), 128 (100), 85 (93), 99 (82), 154 (82), 172 (79), 73 (36), 112 (21), 41 (21).

General Procedure for the Synthesis of *N*-Acyl-ω-amino Ketones from *N*-Acyl Lactams. In a three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet, the N-substituted lactam (**6–9**, 20 mmol) is dissolved in anhydrous THF (70 mL). To that solution, cooled at −78 °C, is added dropwise a solution of the Grignard reagent, prepared in a separate flask from 1-bromohexane or bromobenzene (26 mmol) and magnesium turnings (30 mmol) in THF (30 mL); the reaction mixture is stirred at −78 °C for 3 h and then quenched with 2 N HCl (20 mL). The organic phase is extracted with ether (3 × 50 mL), dried (Na_2SO_4), and evaporated. The products are isolated by flash chromatography, eluting with cyclohexane–ethyl acetate mixtures.

***N*-(4-Oxodecyl)-2,2-dimethylpropanamide (10a)**: mp 26–28 °C; IR (neat) 3370, 1740, 1650 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.2 (s, 9 H), 1.2–2.0 (m, 10 H), 2.4 (m, 4 H), 3.25 (m, 2 H), 5.5 (br, 1 H); MS, *m/e* (relative intensity) 255 (M^+), 57 (100), 128 (87), 155 (60), 85 (44), 102 (44), 142 (43), 170 (41), 43 (33), 41 (30), 85 (27).

***N*-(4-Oxodecyl)benzamide (11)**: mp 79–81 °C; IR (Nujol) 3340, 1720, 1630, 1600 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.1–2.0 (m, 10 H), 2.46 (m, 4 H), 3.45 (m, 2 H), 7.05 (br, 1 H), 7.42 (m, 3 H), 7.8 (m, 2 H); MS, *m/e* (relative intensity) 275 (M^+), 105 (100), 77 (24), 148 (22), 122 (14), 43 (11), 162 (10).

***N*-(4-Phenyl-4-oxobutyl)benzamide (12)**: mp 125–126 °C (lit.[33] mp 125–126 °C); IR (Nujol) 3340, 1750, 1680 cm^{-1}; ^1H NMR δ 2.1 (m, 2 H), 3.12 (t, 2 H), 3.52 (m, 2 H), 6.75 (br, 1 H), 7.45 (m, 6 H), 7.82 (m, 4 H); MS, *m/e* (relative intensity) 267 (M^+), 105 (100), 77 (36), 148 (33), 147 (18), 162 (11), 122 (9).

Benzyl (*N*-(4-oxodecyl)amino)methanoate (13a): mp 42–45 °C; IR (Nujol) 3320, 1690 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.1–2.0 (m, 10 H), 2.4 (m, 4 H), 3.2 (m, 2 H), 4.9 (br, 1 H), 5.1 (s, 2 H), 7.34 (s, 5 h); MS, *m/e* (relative intensity) 305 (M^+, 3), 91 (100), 170 (58), 43 (22), 108 (22), 65 (7), 79 (6).

Benzyl (*N*-(5-oxoundecyl)amino)methanoate (13b): mp 51–53 °C; IR (Nujol) 3340, 1700, 1680 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.1–1.6 (m, 12 H), 2.6 (m, 4 H), 3.6 (q, 2 H), 5.01 (br, 1 H), 5.1 (s, 2 H), 7.3 (5 H); MS, *m/e* (relative intensity) 319 (M^+, 4), 91 (100), 108 (65), 43 (35), 113 (31), 184 (20), 205 (19), 69 (19), 55 (19), 57 (19), 79 (18).

Benzyl (*N*-(4-phenyl-4-oxobutyl)amino)methanoate (14a): mp 76–78 °C; IR (neat) 3370, 1720, 1680 cm^{-1}; ^1H NMR δ 2.0 (m, 2 H), 3.0 (t, 2 H), 3.3 (m, 2 H), 4.92 (br, 1 H), 5.1 (s, 2 H), 7.3 (m, 3 H), 7.52 (m, 2 H); MS, *m/e* (relative intensity) 297 (M^+), 91 (100), 120 (59), 77 (58), 190 (35), 108 (25), 147 (19), 51 (17), 79 (17), 107 (10).

Benzyl (*N*-(5-phenyl-5-oxopentyl)amino)methanoate (14b): mp 66–68 °C; IR (Nujol) 3380, 1725, 1680 cm^{-1}; ^1H NMR δ 1.66 (m, 4 H), 3.0 (t, 2 H), 3.21 (m, 2 H), 5.0 (br, 1 H), 5.1 (s, 2 H), 7.32 (s, 5 H), 7.4–8.0 (m, 5 H); MS, *m/e* (relative intensity) 311 (M^+), 105 (100), 108 (65), 91 (54), 77 (52), 79 (43), 107 (43), 204 (28), 51 (14), 161 (13), 176 (10).

Benzyl (*N*-(5-oxononyl)amino)methanoate (15): mp 35–37 °C; IR (Nujol) 3340, 1720 cm^{-1}; ^1H NMR δ 0.85 (t, 3 H), 1.1–1.7 (m, 8 H), 2.39 (t, 4 H), 3.18 (m, 2 H), 5.1 (s, 2 H), 5.3 (br, 1 H), 7.31 (s, 5 H); MS, *m/e* (relative intensity) 291 (M^+), 91 (100), 57 (20), 41 (20), 65 (14), 56 (12), 39 (11), 85 (10), 108 (8), 156 (8).

***tert*-Butyl (*N*-(4-oxodecyl)amino)methanoate (16a)**: mp 37–39 °C; IR (Nujol) 3380, 1720, 1680 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.2–1.9 (m, 10 H), 1.45 (s, 9 H), 2.42 (m, 4 H), 3.12 (m, 2 H), 4.8 (br, 1 H); MS, *m/e* (relative intensity) 57 (100), 170 (M^+ − Boc, 94), 128 (53), 41 (51), 155 (51), 43 (46), 86 (41), 198 (33), 145 (30), 113 (24).

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tert-Butyl (*N*-(5-oxoundecyl)amino)methanoate (16b): IR (neat) 3380, 1730 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.5 (s, 9 H), 1.1–1.9 (m, 12 H), 2.46 (m, 4 H), 3.15 (m, 2 H), 5.20 (t, 1 H); MS, *m/e* (relative intensity) 57 (100), 43 (43), 41 (33), 56 (30), 184 (M^+ – Boc, 29), 113 (26), 115 (23), 128 (20), 169 (19), 55 (19).

tert-Butyl (*N*-(6-oxododecyl)amino)methanoate (16c): mp 44–46 °C; IR (Nujol) 3380, 1740, 1720, 1690 cm^{-1}; ^1H NMR δ 0.88, t, 3 H), 1.2–1.8 (m, 14 H), 1.45 (s, 9 H), 2.36 (t, 4 H), 3.1 (m, 2 H), 4.52 (br, 1 H); MS, *m/e* (relative intensity) 113 (100), 57 (87), 198 (M^+ – Boc, 84), 129 (48), 86 (43), 41 (41), 226 (36), 142 (28), 140 (24), 59 (22).

tert-Butyl (*N*-(7-oxotridecyl)amino)methanoate (16d): mp 52–54 °C; IR (Nujol) 3340, 1720, 1680 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.1–1.7 (m, 16 H), 1.48 (s, 9 H), 2.4 (t, 4 H), 3.12 (m, 2 H), 4.46 (br, 1 H); MS, *m/e* (relative intensity) 57 (100), 86 (92), 212 (M^+ – Boc, 79), 41 (65), 113 (56), 240 (52), 154 (50), 130 (49), 59 (37), 55 (35).

tert-Butyl (*N*-(4-phenyl-4-oxobutyl)amino)methanoate (17a): mp 96–98 °C; IR (Nujol) 3360, 1720, 1680 cm^{-1}; ^1H NMR δ 1.42 (s, 9 H), 1.9 (m, 2 H), 3.0 (t, 2 H), 3.21 (m, 2 H), 4.73 (br, 1 H), 7.5 (m, 3 H), 7.92 (m, 2 H); MS, *m/e* (relative intensity) 57 (100), 120 (86), 105 (79), 146 (65), 77 (47), 162 (M^+ – Boc, 29), 41 (24), 190 (11).

tert-Butyl (*N*-(5-phenyl-5-oxopentyl)amino)methanoate (17b): mp 88–90 °C; IR (Nujol) 3350, 1720, 1680 cm^{-1}; ^1H NMR δ 1.42 (s, 9 H), 1.6 (m, 4 H), 3.0 (t, 2 H), 3.16 (m, 2 H), 4.6 (br, 1 H), 7.5 (m, 3 H), 7.86 (m, 2 H); MS, *m/e* (relative intensity) 105 (100), 57 (72), 160 (43), 176 (M^+ – Boc, 42), 77 (41), 120 (30), 56 (23), 41 (16).

Di-*tert*-butyl (*N*-(5-oxoundecyl)imino)dimethanoate (26b): IR (neat) 1790, 1745, 1720, 1690 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.1–1.85 (m, 12 H), 2.4 (m, 4 H), 3.6 (t, 2 H); MS, *m/e* (relative intensity) 329 ($M^+ - C_4H_8$), 273 (329 – C_4H_8), 41 (100), 57 (75), 43 (56), 100 (36), 115 (31), 128 (30), 184 (29), 55 (27).

Di-*tert*-butyl (*N*-(6-oxododecyl)imino)dimethanoate (26c): IR (neat) 1790, 1750, 1720, 1690 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.2–1.8 (m, 14 H), 1.51 (s, 18 H), 2.36 (m, 4 H), 3.56 (t, 2 H); MS, *m/e* (relative intensity) 343 ($M^+ - C_4H_8$), 287 (343 – C_4H_8), 57 (100), 129 (28), 43 (27), 41 (24), 113 (18), 198 (17).

Di-*tert*-butyl (*N*-(7-oxotridecyl)imino)dimethanoate (26d): IR (neat) 1790, 1740, 1720 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.1–1.8 (m, 16 H), 1.5 (s, 18 H), 2.38 (t, 4 H), 3.55 (t, 2 H); MS, *m/e* (relative intensity) 357 ($M^+ - C_4H_8$), 301 (357 – C_4H_8), 57 (100), 86 (21), 128 (16), 41 (15), 214 (15), 113 (13).

Di-*tert*-butyl (*N*-(5-phenyl-5-oxopentyl)imino)dimethanoate (27b): mp 73–75 °C; IR (Nujol) 1780, 1735, 1690 cm^{-1}; ^1H NMR δ 1.52 (s, 18 H), 1.7 (m, 4 H), 3.02 (t, 2 H), 3.64 (t, 2 H), 7.5 (m, 3 H), 7.90 (m, 2 H); MS, *m/e* (relative intensity) 321 ($M^+ - C_4H_8$), 265 (321 – C_4H_8), 105 (100), 57 (81), 77 (30), 160 (15), 41 (12).

General Procedure for the Preparation of *N*-Acyl-ω-amino Ketones from Lactams. Synthesis of *N*-(5-Oxoundecyl)-2,2-dimethylpropanamide (10b). In a three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet, 2-piperidinone (**5b**, 1.99 g, 20 mmol) is dissolved in anhydrous THF (60 mL). After cooling at –78 °C, BuLi (2.5 M, 4 mL, 20 mmol) is slowly added to the stirred heterogeneous mixture. After 30 min, a solution of pivaloyl chloride (2.42 g, 20 mmol) in THF (10 mL) is added dropwise, and the reaction mixture is stirred for 2 h at –78 °C. A solution of the Grignard reagent, prepared in a separate flask from 1-bromohexane (4.32 g, 26 mmol) and magnesium turnings (0.72 g, 30 mmol) in THF (30 mL), is then added to the *N*-pivaloyl lactam solution during 10 min. The mixture is stirred for 3 h and then quenched with 2 M HCl (20 mL), and the organic phase is extracted with ether (3 × 50 mL), washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated to leave **10b** (5.22 g, 97%), more than 95% pure by TLC, GC, and spectroscopic analysis: IR (neat) 3360, 1720, 1640 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.21 (s, 9 H), 1.2–1.7 (m, 12 H), 2.4 (m, 4 H), 3.22 (q, 2 H), 6.3 (br, 1 H); MS, *m/e* (relative intensity) 269 (M^+), 57 (100), 41 (65), 43 (64), 69 (42), 142 (39), 85 (30), 56 (28), 100 (24), 169 (22).

General Procedure for the Deprotection of *N*-Boc-ω-amino Ketones. Synthesis of Cyclic Imines. Trifluoroacetic acid (8 mL) is added dropwise to the *N*-Boc-ω-amino ketone (**16a–c**, **17a,b**) (10 mmol) with stirring (magnetic bar) at 0 °C. The solution is stirred at room temperature for 3 h, and than a 30% aqueous solution of sodium hydroxide is carefully added, with cooling at 0 °C, until pH 10–11 is reached. The organic base is extracted with ether (3 × 30 mL), washed with brine, dried (Na_2SO_4), and evaporated. The crude imine is purified by flash chromatography, eluting with cyclohexane–ethyl acetate mixtures.

3,4-Dihydro-5-hexyl-2*H*-pyrrole (30a): IR (neat) 1640 cm^{-1}; UV (hexane) λ_{max} 226 nm (ϵ 172); ^1H NMR δ 0.9 (t, 3 H), 1.1–1.9 (m, 10 H), 2.38 (m, 4 H), 3.81 (m, 2 H); ^{13}C NMR δ 178.45, 60.8, 37.2, 33.9, 31.7, 29.3, 26.5, 22.65, 14.1; MS, *m/e* (relative intensity) 153 (M^+), 83 (100), 97 (70), 110 (48), 84 (30), 41 (27), 98 (21), 55 (15), 124 (14), 68 (11).

2,3,4,5-Tetrahydro-6-hexylpyridine (30b): IR (neat) 1665 cm^{-1}; UV (hexane) λ_{max} 214 nm (ϵ 1014); ^1H NMR δ 0.89 (t, 3 H), 1.1–1.8 (m, 12 H), 2.1 (m, 4 H), 3.55 (m, 2 H); ^{13}C NMR δ 171.75, 48.9, 41.0, 31.75, 29.2, 29.0, 26.6, 22.6, 21.95, 19.6, 14.05; MS, *m/e* (relative intensity) 167 (M^+), 97 (100), 96 (15), 41 (14), 110 (10), 55 (10), 82 (7).

3,4,5,6-Tetrahydro-7-hexyl-2*H*-azepine (30c): IR (neat) 1660 cm^{-1}; UV (hexane) λ_{max} 212 nm (ϵ 313); ^1H NMR δ 0.88 (t, 3 H), 1.1–1.9 (m, 14 H), 2.3 (m, 4 H), 3.6 (t, 2 H); ^{13}C NMR δ 178.5, 51.9, 43.0, 33.2, 31.75, 29.3, 26.65, 26.25, 23.7, 22.65, 14.05; MS, *m/e* (relative intensity) 181 (M^+), 11 (100), 124 (26), 83 (14), 112 (14), 96 (13), 110 (12), 138 (10), 41 (10) (little amounts of the corresponding amino ketone were revealed by the absorptions at 3400 and 1720 cm^{-1} in the IR spectrum).

General Procedure for the Synthesis of Cyclic Imines from Lactams. Synthesis of γ-Coniceine (32). In a three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet, a solution of 2-piperidinone (**5b**, 2.98 g, 30 mmol) in anhydrous THF (80 mL) is cooled at –78 °C, and then BuLi (2.5 M, 12 mL, 30 mmol) is added dropwise with stirring. The mixture is stirred for 30 min, then a solution of di-*tert*-butyl dicarbonate (6.55 g, 30 mmol) in THF (10 mL) is slowly added, and the stirring is continued for 3 h at –78 °C. A solution of the Grignard reagent, prepared from 1-bromopropane (4.84 g, 39 mmol) and magnesium turnings (1.08 g, 45 mmol) in THF (40 mL), is then added during 15 min, and the mixture is stirred at –78 °C for 3 h. After quenching with 2 N HCl (30 mL) and extraction with ether (3 × 80 mL), the organic phase is washed with 10% aqueous $NaHCO_3$ and then with brine, dried (Na_2SO_4), and evaporated at reduced pressure. To the residue is slowly added TFA (25 mL) at 0 °C, the mixture is magnetically stirred at room temperature for 3 h, then 30% aqueous NaOH is added at 0 °C to reach pH 10–11, and the organic base is extracted with ether (3 × 60 mL), washed with brine, dried (Na_2SO_4), and evaporated at normal pressure. Distillation of the residue yields **32**[15b,29b,37] (1.65 g, 44% yield), bp 72–75 °C (24 mmHg) (lit.[15b] bp 84–85 °C (36 mmHg)). The other cyclic imines prepared (**30a**, **31a**, **33**[38]) were isolated by flash chromatography.

General Procedure for the Synthesis of Pyridyl-Substituted Cyclic Imines. Synthesis of Apoferrorosamine (37). In a three-necked, round-bottomed flask equipped with a mechanical stirrer and an argon inlet, 2-bromopyridine (3.18 g, 20 mmol) is dissolved in ether (50 mL). To the stirred solution, cooled at –90 °C, is added BuLi (2.5 M, 8 mL) dropwise, and the mixture is further stirred for 20 min; then a solution of **9a** (3.70 g, 20 mmol) in THF (30 mL) is slowly added, and the stirring is continued for 3 h at –90 °C. After quenching with 2 M HCl (20 mL) and extraction with ether (3 × 60 mL), the organic phase is washed with 10% aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4), and evaporated. The treatment of the crude organic product (**35**) with TFA (15 mL) at 0 °C, then at room temperature for 3 h, followed by the addition of 30% aqueous NaOH to reach pH 10–11, extraction with ether (3 × 50 mL), drying (Na_2SO_4), evaporation at reduced pressure, and flash chromatography of the residue, eluting with a cyclohexane–ethyl acetate mixture (90:10), affords the apoferrorosamine (**37**,[4c,27,39] 1.84 g, 63% yield) as an oil, which slowly crystallizes: mp 44–46 °C (lit.[39] mp 46–48 °C).

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Registry No. **5a**, 616-45-5; **5b**, 675-20-7; **5c**, 105-60-2; **5d**, 673-66-5; **6a**, 51269-69-3; **7**, 2399-66-8; **8a**, 14468-80-5; **8b**, 106412-35-5; **9a**, 85909-08-6; **9b**, 85908-96-9; **9c**, 106412-36-6; **9d**, 116437-30-0; **10a**, 116437-31-1; **10b**, 116437-32-2; **11**, 116437-33-3;

12, 76866-96-1; **13a**, 116437-34-4; **13b**, 116437-35-5; **14a**, 69352-30-3; **14b**, 116437-35-5; **15**, 116437-36-6; **16a**, 116437-37-7; **16b**, 116437-38-8; **16c**, 116437-39-9; **16d**, 116437-40-2; **17a**, 116437-41-3; **17b**, 116437-42-4; **18**, 1671-75-6; **19**, 5454-21-7; **20**, 120-51-4; **21**, 10361-39-4; **22**, 41084-78-0; **26b**, 116437-43-5; **26c**, 116437-44-6; **26d**, 116437-45-7; **27**, 116437-46-8; **30a**, 116437-48-0; **30b**, 5832-25-7; **30c**, 116437-49-1; **31a**, 700-91-4; **31b**, 57050-07-4; **32**, 1604-01-9; **33**, 95018-40-9; **36a**, 532-12-7; **36b**, 3471-05-4; **37**, 4593-27-5; *t*-BuCOCl, 3282-30-2; PhCOCl, 98-88-4; $PhCH_2OCOCl$, 501-53-1; $(t\text{-BuOCO})_2O$, 24424-99-5; *n*-$C_6H_{13}Br$, 111-25-1; PhBr, 108-86-1; *n*-BuLi, 109-72-8; $H_3C(CH_2)_5CO(CH_2)_5NH_2$, 116466-11-6; *n*-$C_{11}H_{23}Br$, 693-67-4; 2-bromopyridine, 109-04-6; 3-bromopyridine, 626-55-1; 1-aminotridecan-7-one, 116437-47-9; 1-bromopropane, 106-94-5; benzyl alcohol, 100-51-6.

Isolation and Structure Elucidation of Seven New Polyhydroxylated Sulfated Sterols from the Ophiuroid *Ophiolepis superba*†

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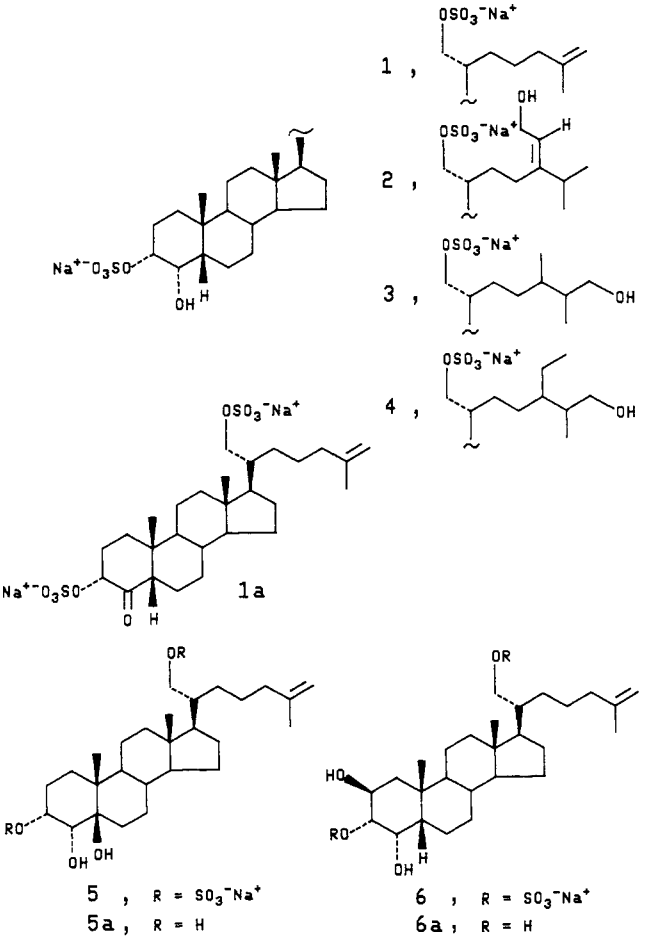
Seven new polyhydroxylated sulfated sterols, all possessing 3α,21-disulfoxy-4α-hydroxy substituents and the A/B cis ring junction, have been isolated from the ophiuroid *Ophiolepis superba*, collected at Okinawa, Japan. Four sterols possessed identical nuclei (i.e., 3α-sulfoxy-4α-hydroxy) but differed in the side chain. Two possessed one more hydroxyl group in the nucleus located at C-2β, and one had the extra hydroxyl group at C-5β. Their general structure was deduced from spectral data (^1H and ^{13}C NMR and FABMS), and the stereochemistry of some of them was determined by correlating their respective spectral data with those of synthetic sterols.

Sterols with hydroxy and sulfoxy functionalities have been recently reported from marine ophiuroids (commonly known as brittle stars). Apart from a group of 5α-H steroids possessing 2β,3α,26-trisulfoxy substituents, isolated from *Ophiorachna incrassata*,[1] all the isolated polyhydroxylated sulfated sterols possessed a 21-sulfoxy substituent. 5β-Cholestane-3α,4α,11β,21-tetrol 3,21-disulfate (**8**) is the major polar steroid component of the Pacific *Ophiocoma dentata*, *O. incrassata*, and *Ophiarthrum elegans*, the latter of which also contained the 11-keto derivative.[1] The Mediterranean *Ophioderma longicaudum* contained a group of cytotoxic disulfated 3α,21-dihydroxy-5α-H steroids along with the moderately cytotoxic 5β-cholestane-3α,4α,11β,12β,21-pentol 3,21-disulfate.[2]

Our investigation of the Pacific ophiuroid *Ophiolepis superba* collected near Zampa, Okinawa, led to the isolation of seven new polyhydroxylated sulfated sterols (**1–7**), all with 3α,21-disulfoxy-4α-hydroxy substituents and the A/B cis ring junction. The polar sterol mixture also contained the known **8**[1] and **9**.[2]

Since spectral data indicated that the steroids **1–4** possessed virtually identical nuclei and the same 21-sulfoxy substituent, but differed in the side chain, it was only necessary to settle the nuclear substitution pattern of the steroid **1**.

Structure Elucidation of 5β-Cholest-25-ene-3α,4α,21-triol 3,21-Disulfate (1). The negative-ion fast atom bombardment (FAB) mass spectrum exhibited molecular ion species at *m/z* 577, 599 (major), and 615, corresponding to $[M(SO_3H)SO_3^-]$, $[M(SO_3Na)SO_3^-]$, and [M-



†This paper is dedicated to Professor Edgar Lederer (Gif-Sur-Yvette, France) on the occasion of his 80th birthday.

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