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A FACILE AND EFFICIENT METHOD FOR MACROLACTAMIZATION

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Summary : Using 2-bromo-1-methylpyridinium iodide as carboxyl activating agent, 10 ansa-macrolactams were prepared conveniently from the corresponding seco-precursor ω-amino acids. In most cases the yields are excellent.

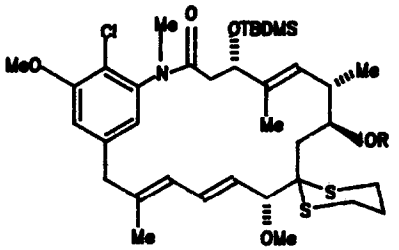
Although there have been a number of methods [1] developed for the preparation of amides, those suitable to macrocyclic lactamization of multifunctionalized long chain amino acid precursors are comparatively scarce.[2] Mukaiyama and co-workers [3] reported that 2-halo-1-methylpyridinium iodide as carboxyl activating agent could be used for the preparation of esters, amides and lactones. In a study on the total synthesis of maytansinoids [4], the authors found it very convenient and efficient to use 2-halo-1-methylpyridinium iodide in the construction of the macro-ring of maytansinoids 1 from the seco-precursors 2 in a yield around 70%.

In order to ascertain the generality of this method to macrolactamization, the preparation of a series of macrolactams (3, 4, 5) from the corresponding ω-amino acids (6, 7, 8) has been undertaken. The results show that almost in every case the yield was over 80% (Table 1), provided the length of the side chain was sterically feasible for the ansa-macrolactamization.

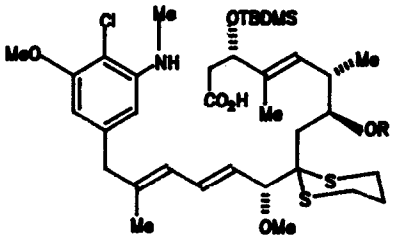
The seco-precursors 6, 7 and 8 were prepared as follows.

The phosphonium salts 9 were obtained from the corresponding methyl ω-iodoalkanoates and triphenylphosphine in refluxing benzene. In the subsequent Wittig reaction of p-trifluoroacetamido-benzaldehyde and phosphonium salts 9 to yield the methyl alkenoate 10 and 11, sodium methoxide was used as a deprotonating agent for 9.[5] It was interesting that in MeOH-DMF solvent the predominating product (95%) was in E-form, and in the absence of methanol the predominating product was in Z-form.[6] The methyl alkenoates 10 and 11 were hydrogenated in the presence of Pd-C to give methyl alkanoates 12.

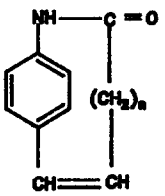
Esters 10, 11 and 12 were hydrolyzed respectively in 5% aq. methanolic sodium hydroxide, and then neutralized with aq. NaH_2PO_4 to afford carboxylic acids 6, 7 and 8.

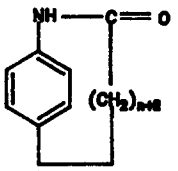


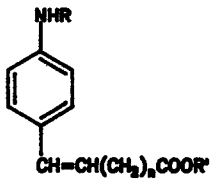
1 R=EE, MEM

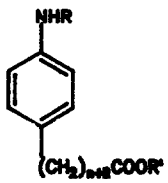


2 R=EE, MEM









3(Z)- 4(E)-

3a: n=8

3b: n=9

3c: n=10

4a: n=9

4b: n=10

5

5a: n=6

5b: n=7

5c: n=8

5d: n=9

5e: n=10

6 R=R'=H, (Z)-, n=7-10

7 R=R'=H, (E)-, n=6,8,9,10

10 R=$COCF_3$, R'=Me, (Z)-, n=7-10

11 R=$COCF_3$, R'=Me, (E)-, n=6,8,9,10

8 R=R'=H, n=6-10

12 R=$COCF_3$ R'=Me, n=6-10

$Ph_3P^+CH_2(CH_2)nCOOMe\ I^-$

9

Macrolactamization of 6, 7 and 8 was carried out in 1,2-dichloroethane. In the process, the seco-precursor and tri-n-butylamine were added slowly and uniformly to 2-bromo-1-methylpyridinium iodide in a period of 10 hrs at 35°C. The yields of macrolactams 3, 4 and 5 are listed in Table 1, ranging from 78-92% except that of 4a.

Table 1. The yields and mps of ansa-macrolactams

Compound	Isolated Yield%	mp°C	Compound	Isolated Yield%	mp°C
3a	87	156-157	5a	78	142-143
3b	86	133-134	5b	85	143-144
3c	88	137-138	5c	92	144-145
4a	56	144-146	5d	83	145-146
4b	82	171-172	5e	88	149-150

The ring tension of 4a might account for its relatively low yield. No success of lactamization of 6a, 7a and 7b is in accordance with the failure of constructing the respective lactam models (3 n=7; 4 n=6,8).[7]

The addition duration of the seco-precursors would control the probability of intermolecular reaction . So its influence upon the yields was examined during the preparation of 5a, 5c and 5e. It was shown that variation of the addition duration from 10 to 3 hrs did not decrease the yields, but the yields reduced to one third by one portion addition.

Of the last few steps macrolactamization is the critical one for the total synthesis of the natural macrocyclic lactams. The present method is of general utility for macrolactamization, and is superior or comparable to other activated amino acid methods reported [8, 9] in that it provides pure products in excellent yields under simple and mild conditions, and offers easy work-up.

Procedure for the macrolactamization: Using a motor driven syringe, a solution of 0.10 mmol of 6, 7 or 8 and 0.13 ml (0.55 mmol) tri-n-butylamine in 5ml of 1,2-dichloroethane was added uniformly to a suspension of 80mg (0.27 mmol) of 2-bromo-1-methylpyridinium iodide in 15ml of 1,2-dichloroethane at 35°C under argon over a period of 10 hrs. After standing overnight, the solvent was removed and the residue was taken into ether. The solution was washed with 1N hydrochloric acid and water, dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated in vacuum to dryness, and the residue obtained was chromatographed on silica gel

with ether-petroleum ether (2:1) as an eluent to give macrolactam 3, 4 or 5. All the lactams gave satisfactory IR, ^{1}HNMR, MS and elementary analysis data.[10]

Acknowledgment : This work was supported by a grant from the National Natural Science Foundation of China.

References and Notes

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10. ^{1}HNMR (400MHZ, $CDCl_3$) and MS data of reprensentative examples. 3a: 0.50 (m, 2H), 0.64-1.39 (m, 10H), 2.20-2.28 (m, 4H), 5.70 (dt, 1H, J=11.2, 8.5), 6.64(d,1H, J=11.2), 7.18(d, 2H, J=8.1), 7.26(d, 2H, J=8.1), 7.45(brS, 1H); MS m/e 257 (M^+). 4b: 0.42(m,2H), 0.82(m,2H), 0.90-1.08(m, 6H), 1.23-1.35(m, 4H), 2.52(m, 2H), 2.08(m, 2H), 2.25(m,2H), 6.15(dt, 1H, J=15.7, 7.7), 6.33(d, 1H, J=15.7), 7.13(d, 2H, J=8.3), 7.26(s,1H), 7.36(d, 2H, J=8.3); MS m/e 285(M^+). 5a: -0.10(m, 2H), 0.76(m, 2H), 1.03-1.19(m, 6H), 1.54(m, 2H), 2.20(m, 2H), 2.69(t, 2H, J=6.4), 7.15(d, 2H, J=8.0), 7.22(d, 2H, J=8.0), 7.42(S, 1H); MS m/e 231(M^+).

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