# The Total Synthesis of (+)-Macbecin I

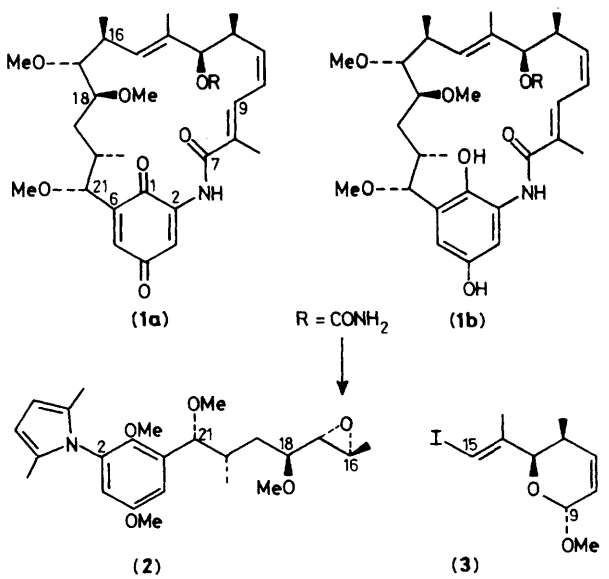
**Raymond Baker* and Jose L. Castro**

*Chemistry Department, Merck Sharp & Dohme Research Laboratories Ltd., Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow CM20 2QR, Essex*

Reaction of a higher order cyanocuprate, derived from a vinyl iodide, with a chiral epoxide has been used as the basis of the first total enantioselective synthesis of (+)-macbecin I.

Macbecin I (**1a**) and II (**1b**) are antitumor antibiotics isolated from the fermentation broth of an actinomycete, *Nocardia sp.* (no. C-14919).[1] The structure and absolute configuration of these compounds has been determined by Muroi *et al.*[2] from partial degradation studies and *X*-ray crystallographic analysis and they were assigned to the ansamycin group of antibiotics, which also includes geldanamycin,[3] herbimycin,[4] and ansamitocin.[5] The macbecins are moderately active against several Gram-positive bacteria and fungi and both show marked antitumor activity against leukemia P388, melanoma B16, and Ehrlich carcinoma *in vivo*.[6] Although some efforts have been directed towards the synthesis of macbecin,[7] this report represents the first total asymmetric synthesis of (+)-macbecin I.

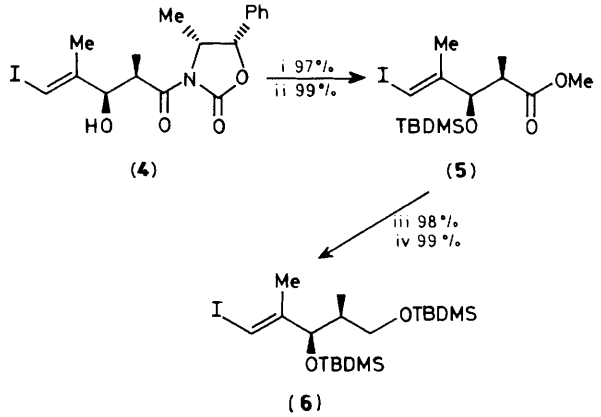
Our retrosynthetic analysis of macbecin involves disconnection between the C(15)–C(16) bond to give rise to epoxide (**2**)[8] and vinyl iodide (**3**),[9] prepared as previously described. The plan was to couple these two fragments together by ring opening of epoxide (**2**) with a higher order cyanocuprate derived from (**3**).[10] In spite of extensive efforts, however, we were unable to obtain any of the desired product, with only reduced vinyl iodide and its corresponding dimer being isolated. The same fruitless results were obtained by using the corresponding aluminate of (**3**) ($Bu^tLi$, $Me_3Al$).[11] The most obvious modification to overcome the low reactivity of the 2,3-disubstituted epoxide would be to utilise Lewis acid catalysis in the reaction.[12] This would be, however, incompatible with the reactivity of the α,β-unsaturated methoxy lactol moiety in (**3**).[13] Based on previous reports[14] the use of a vinyl



iodide such as (**6**) appeared to represent an alternative strategy. Preparation of (**4**) has been previously reported[9] and this was converted in four steps to (**6**). The chiral auxiliary in (**4**) was removed under the usual conditions (NaOMe, $MeOH–CH_2Cl_2$) and the hydroxyl group protected as the t-butyldimethylsilyl (TBDMS) derivative (TBDMS–OTf, 2,6-lutidine) to give ester (**5**). Reduction of the ester [di-isobutylaluminium hydride (DIBAL-H), −33 °C) followed by silylation of the primary alcohol (TBDMS–Cl, imidazole–dimethylformamide) afforded the bis-silylated compound (**6**) (Scheme 1).

Although reaction of epoxide (**2**) with the higher order cyanocuprate derived from (**6**) (2 equiv. $Bu^tLi$, −80 °C, 2 h; 1/2 equiv. CuCN, −78 to −10 °C, 15 min) gave less than 5% of the coupled product (**7**) after 48 h at −30 °C, addition of $BF_3·OEt_2$ (2 equiv.) to a −78 °C solution of the epoxide and cuprate in $Et_2O$ afforded, after 1 h at −78 °C an 84% isolated yield of (**7**) (Scheme 2). Some iodohydrin (12%) was also observed. The hydroxy group was then methylated [NaH, MeI, tetrahydrofuran (THF), 25 °C] to give (**8**) in excellent yield. At this stage nuclear Overhauser enhancement (n.O.e.) experiments demonstrated that the alkene geometry had been preserved during the cuprate coupling. Thus, irradiation of the alkenic proton 15-H produced a signal enhancement of n.O.e. in 13-H and 17-H but not in the 14-Me.† Selective removal of the primary silyl group was successfully achieved (95% yield) by using a mixture of 1 : 3 : 3 HF·Py–Py–THF in MeOH at room temperature for 6 h. In order to introduce the (*Z*) C(11)–C(10) double bond, alcohol (**9**) was oxidised to the aldehyde (89% yield) with $SO_3·Py$ in dimethyl sulphoxide (DMSO)[15] and this was reacted with the potassium anion [$KN(SiMe_3)_2$, THF, −78 °C] of methyl bis-(2,2,2-trifluoroethyl)phosphonoacetate [$(CF_3CH_2O)_2P(O)CH_2CO_2Me$] in the presence of 18-crown-6 (2.5 equiv.) at −78 °C to give a 99% isolated yield of the required (*Z*)-alkene (**10**).[16] Reduction of the ester with DIBAL–H at −33 °C cleanly afforded the allylic alcohol (**11**).

In view of the nature of the nucleophilic conditions required for removal of the pyrrole moiety[17] we decided to remove the protecting group. However, disappointing results were obtained by refluxing (**11**) with $H_2NOH·HCl$ in aq. EtOH, with only desilylation being observed after 16 h. Under more forcing conditions [$H_2NOH·HCl$ (30 equiv.), KOH (20 equiv.), 2 : 1 $EtOH–H_2O$, reflux, 68 h], a 70% isolated yield of (**12**) was obtained, together with 25% recovered (**11**). In this way one of the steps which had given apprehension had been achieved. The nitrogen group of (**12**) was reprotected as the trifluoracetamide under usual conditions to give (**13**) in 95% yield. Oxidation of the allylic alcohol to the corresponding aldehyde presented more problems than anticipated. Thus, $SO_3·Py–DMSO$ failed to give reasonable yields of the aldehyde and activated manganese dioxide afforded only a moderate (65%) yield of the aldehyde with extensive decomposition. Satisfactory oxidation was achieved with pyridinium dichromate (PDC)[12] in $CH_2Cl_2$ at 25 °C, although a small amount (9%) of (*Z*) to (*E*) isomerisation of the C(11,10) double bond occurred during the reaction. The separation of the isomers was not possible at this stage but was achieved after the next step. Thus, this aldehyde mixture was reacted with (ethoxycarbonylethylidene)triphenylphosphorane ($Ph_3P=CMeCO_2Et$; 2 equiv.) in $CH_2Cl_2$ to give, after flash chromatography, an 83% isolated yield (two steps) of pure (*Z*, *E*)-diene (**14**).

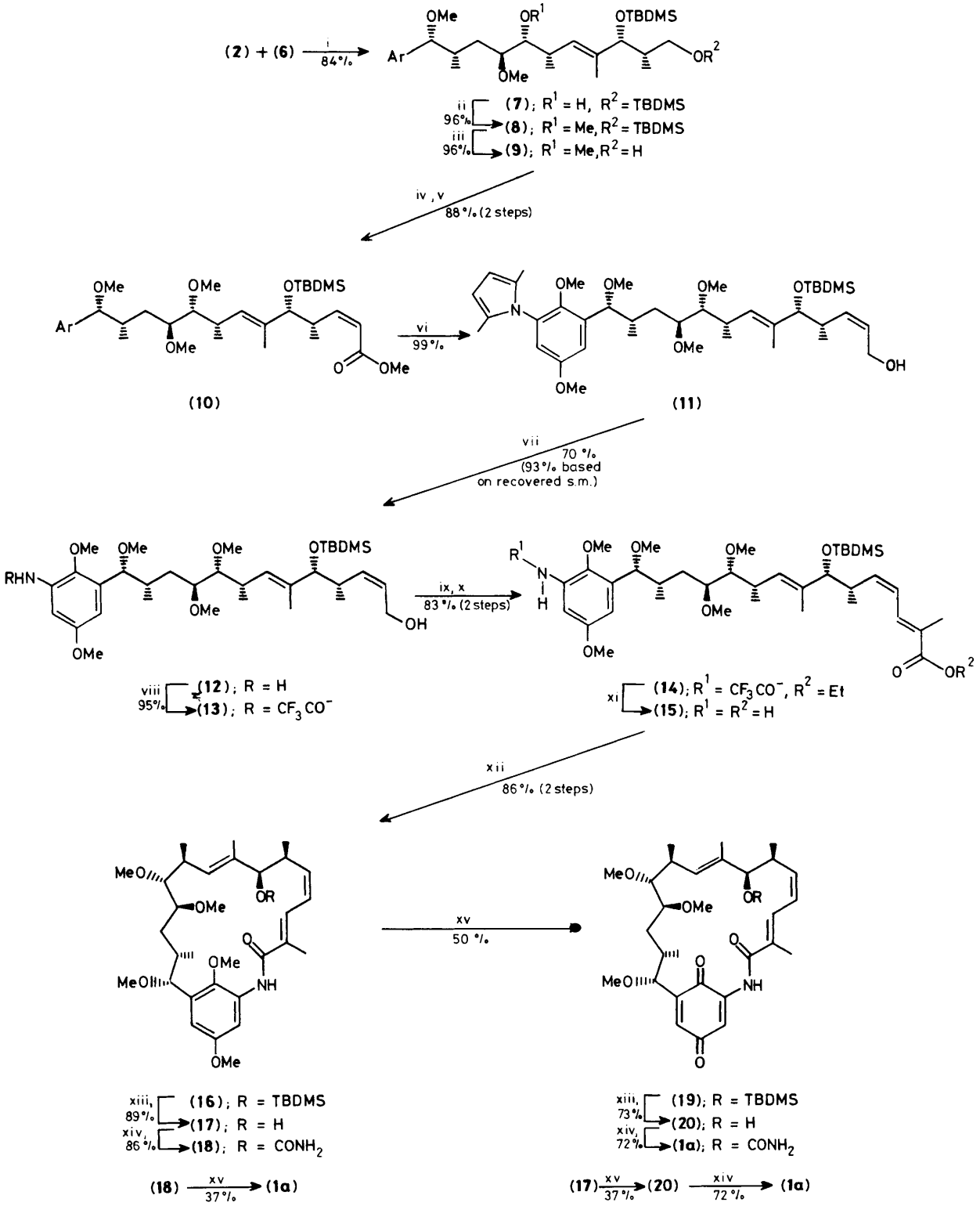



**Scheme 1.** *Reagents and conditions:* i, NaOMe (1.1 equiv.), $MeOH–CH_2Cl_2$, −23 °C, 20 min; ii, TBDMS–OTf (1.5 equiv.), 2,6-lutidine (2.5 equiv.), $CH_2Cl_2$, 0 °C, 1.5 h; iii, DIBAL–H, (2.6 equiv.), toluene, −20 °C, 1.5 h; iv, TBDMS–Cl (1.5 equiv.), imidazole (3.0 equiv), dimethylformamide (DMF), 25 °C, 17 h.

† Macbecin numbering is used.

We had now arrived at the crucial stage of the synthesis, since removal of the trifluoracetamido protecting group and hydrolysis of the ester would yield amino acid (**15**) required for macrolactamisation. Reaction of (**14**) with LiOH in $MeOH–H_2O$ gave amino acid (**15**). This was easily extracted from water (pH 5) and used in the next step without further purification after being azeotropically dried with toluene. Macrocyclisation was achieved after only four attempts. Thus, although the use of DCC, diethyl cyanophosphonate[19] and diphenylphosphoryl azide[20] did not induce the required ring closure reaction, this was successfully achieved by reaction in the presence of mesitylenesulphonyl chloride[21] or bis-(2-oxo-3-oxazolidinyl)phosphinic chloride.[23] Syringe pump addition of a solution of (**15**) (1 mg/ml) and di-isopropylethylamine (2 equiv.) in toluene to a $10^{-2}$ M solution of mesitylenesulphonyl chloride and $Pr^i_2NEt$ (20 equiv. each) in toluene at 65 °C gave, after 14 h, a 71% isolated yield of (**16**). Alternatively, reaction of (**15**) with bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (4 equiv.) and $Pr^i_2NEt$ (10 equiv.) in toluene ($1.5 \times 10^{-3}$ M) afforded an 85% isolated yield of (**16**) after 15 h at 85 °C. We are impressed by the simplicity and efficiency of the application of the second set of conditions, since they had not, as far as we are aware, been previously employed for macrocyclisation.[22] We had, therefore, achieved one of our major goals and were left with finding a procedure for incorporation of the carbamate moiety at C(13) and a final oxidation to the quinone.

Three alternative pathways were considered and followed. Introduction of the carbamate group could precede oxidation or the reverse. In the first approach the TBDMS protecting group in (**16**) was removed under the usual conditions [tetrabutylammonium fluoride (TBAF), THF, 25 °C] to give (**17**) in 89% yield. Although carbamoylation of (**17**) could not be achieved by reaction with phosgene and ammonia quenching,[23] treatment of (**17**) with sodium cyanate (12 equiv.) and trifluoroacetic acid (12 equiv.) in dichloromethane gave the required carbamate (**18**) in 86% yield after 3 h at 25 °C.[24] Oxidation of (**18**) with cerium(IV) ammonium nitrate[25] (CAN) (3 equiv.) in $MeOH–H_2O$ at 0 °C for 10 min afforded macbecin I (**1a**) in 37% isolated yield. Comparable yields (32%) of (**1a**) were obtained when silver(II) dipicolinate[26] was used as the oxidising agent. Alternatively, oxidation of (**16**) with CAN as previously described afforded quinone (**19**) in 50% isolated yield, which was converted into macbecin I (**1a**) by desilylation (72.5% yield) and carbamoylation (71.5% yield). In addition, quinone (**20**) was also prepared in 37% yield by CAN oxidation of (**17**) as above.



**Scheme 2.** *Reagents and conditions:* i, (**6**) (2.4 equiv.), Bu$^t$Li (4.8 equiv.), −80 °C, 2 h; CuCN (1.2 equiv.), −78 to −10 °C, 15 min; (**2**) (1.0 equiv.), $BF_3$·$OEt_2$ (2.0 equiv.), −78 °C, 1 h; ii, NaH (1.3 equiv.), MeI (5.0 equiv.), THF, 6 h; iii, 1:3:3 HF·Py–Py–THF (20 equiv. HF), MeOH, 25 °C, 6.5 h; iv, $SO_3$·Py (7.0 equiv.), $Et_3N$ (15 equiv.), THF–DMSO, 25 °C, 1.5 h (89%); v, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (1.15 equiv.), 18-crown-6 (2.5 equiv.), $KN(SiMe_3)_2$ (1.1 equiv.), THF, −78 °C, 1 h (99%); vi, DIBAL–H (2.6 equiv.), toluene, −33 °C; vii, $H_2NOH$·HCl (30 equiv.), KOH (20 equiv.), 2:1 EtOH–$H_2O$, reflux, 68 h; viii, TFAA (3.0 equiv.), $Et_3N$ (6.0 equiv.), $CH_2Cl_2$, 0—25 °C, 1 h; pH 7 phosphate buffer, MeOH, 25 °C, 15 min; ix, PDC (2.0 equiv.), $CH_2Cl_2$, 16 h; x, $Ph_3P{=}C(Me)CO_2Et$ (2.0 equiv.), $CH_2Cl_2$, 40 °C, 40 h; xi, LiOH (10 equiv.), 2:2:1 THF–MeOH–$H_2O$, 25 °C, 24 h; xii, bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (4.0 equiv.), $Pr^i_2NEt$ (10 equiv.) toluene, 85 °C, 15 h; xiii, TBAF (5 equiv.), THF, 25 °C, 40 h; xiv, NaOCN (12 equiv.), TFA (12 equiv.), 0—25 °C, 3 h; xv, CAN (3 equiv.), MeOH–$H_2O$, 0 °C, 10 min.

Thus, the first enantioselective synthesis of (+)-macbecin I (**1a**) {m.p. 205—206 °C (softening at 176 °C), EtOH–$H_2O$; $[\alpha]_D$ = +377° ($c$ = 0.10, $CHCl_3$)}‡ has been achieved in 2.5% overall yield. Since macbecin I has been converted to macbecin II this also constitutes a formal synthesis of the latter.

J. L. Castro thanks M.S.D.R.L. (Harlow, U.K.) for the provision of facilities and the Ministry of Education and Science (Spain) and British Council for a grant. We acknowledge the contribution of Dr. C. Swain for valuable advice and discussion.

*Received, 20th October 1988; Com. 8/04157A*

## References

1 S. Tanida, T. Hasegawa, and E. Higashide, *J. Antibiot.*, 1980, **33**, 199.
2 M. Muroi, K. Haibara, M. Asai, and T. Kishi, *Tetrahedron Lett.*, 1980, **21**, 309; M. Muroi, K. Haibara, M. Asai, K. Kamiya, and T. Kishi, *Tetrahedron*, 1981, **37**, 1123.
3 C. DeBoer, P. A. Meulman, R. J. Wnuk, and D. H. Peterson, *J. Antibiot.*, 1970, **23**, 442.
4 S. Omura, Y. Iwai, Y. Takahashi, N. Sadakane, and A. Nakagawa, *J. Antibiot.*, 1979, **32**, 255.
5 S. Tanida, T. Hasegawa, K. Hatano, E. Higashide, and M. Yoneda, *J. Antibiot.*, 1980, **33**, 192.
6 M. Muroi, M. Izawa, Y. Kosai, and M. Asai, *J. Antibiot.*, 1980, **33**, 205.
7 D. A. Evans, P. L. Ornstein, and M. D. Ennis, 187th ACS Natl. Meeting (Apr 8–13, St. Louis) 1984; MEDI-154.
8 R. Baker and J. L. Castro, *J. Chem. Soc., Perkin Trans. I.*, in press.
9 R. Baker, W. J. Cummings, J. F. Hayes, and A. Kumar, *J. Chem. Soc., Chem. Commun.*, 1986, 1237.
10 B. H. Lipshutz, *Synthesis*, 1986, 325 and references therein.
11 M. Kobayashi, L. F. Valente, E. Negishi, W. Patterson, and A. Silveira, Jr., *Synthesis*, 1980, 1034; A. Pfaltz and A. Mattenberger, *Angew. Chem., Int. Engl.*, 1982, **21**, 71.
12 A. Alexakis, D. Jachiet, and J. F. Normant, *Tetrahedron*, 1986, **42**, 5607; Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 947; M. J. Eis, J. E. Wrobel, and B. Ganem, *J. Am. Chem. Soc.*, 1984, **106**, 3693; B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, and S. L. Nguyen, *Tetrahedron Lett.*, 1984, **25**, 5959.
13 A. Ghribi, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, 1984, **25**, 3079; 1984, **25**, 3083; 1984, **25**, 3075.
14 T. Takahashi, Y. Naito, and J. Tsuji, *J. Am. Chem. Soc.*, 1981, **103**, 5261; E. J. Corey and D. J. Beames, *ibid.*, 1972, **94**, 7210; C. C. Howard, R. F. Newton, D. P. Reynolds, A. H. Wadsworth, D. R. Kelly, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. I.*, 1980, 852; J. P. Marino and M. G. Kelly, *J. Org. Chem.*, 1981, **46**, 4389; D. Culshaw, P. Grice, S. V. Ley, and G. A. Strange, *Tetrahedron Lett.*, 1985, **26**, 5837.
15 J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.
16 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405.
17 S. P. Bruekelman, S. E. Leach, G. D. Meakins, and M. D. Tirel, *J. Chem. Soc., Perkin Trans. I.*, 1984, 2801; S. P. Findley, *J. Org. Chem.*, 1956, **21**, 644.
18 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
19 For a successful macrolactamisation using this reagent in rifamycin synthesis see: E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 1980, **21**, 2045; H. Iio, H. Nagaoka, and Y. Kishi, *J. Am. Chem. Soc.*, 1980, **102**, 7965.
20 T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
21 This reagent has been used in the synthesis of *N*-methylmaysenine and maytansine: E. J. Corey, L. O. Weigel, A. R. Chamberlin, and B. Lipshutz, *J. Am. Chem. Soc.*, 1980, **102**, 1439; E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho, and D. H. Hua, *ibid.*, 1980, **102**, 6613.
22 For preparation of amides using this phosphorus reagent see: J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernandez-Lizarbe, and A. Zugaza-Bilbao, *Synthesis*, 1980, 547.
23 Y. Kishi, *J. Nat. Prod.*, 1979, **42**, 549.
24 B. Loev and M. F. Kormendy, *J. Org. Chem.*, 1963, **28**, 3421.
25 See for example: M. Shiraishi and S. Terao, *J. Chem. Soc., Perkin Trans. I.*, 1983, 1591.
26 K. Kloc, J. Mlochowski, and L. Syper, *Chem. Lett.*, 1980, 725.

‡ The spectroscopic properties of synthetic (**1a**) were in full agreement with those published in the literature (Reference 2). The reported melting point and optical rotation for macbecin I is 187—8 °C (decomp.) (no solvent specified) and $[\alpha]_D$ = +351° ($c$ = 0.10, $CHCl_3$).