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An enantiospecific synthesis of (+)-demethoxyerythratidinone from (*S*)-malic acid: key observations concerning the diastereocontrol in malic acid-derived *N*-acyliminium ion cyclisations

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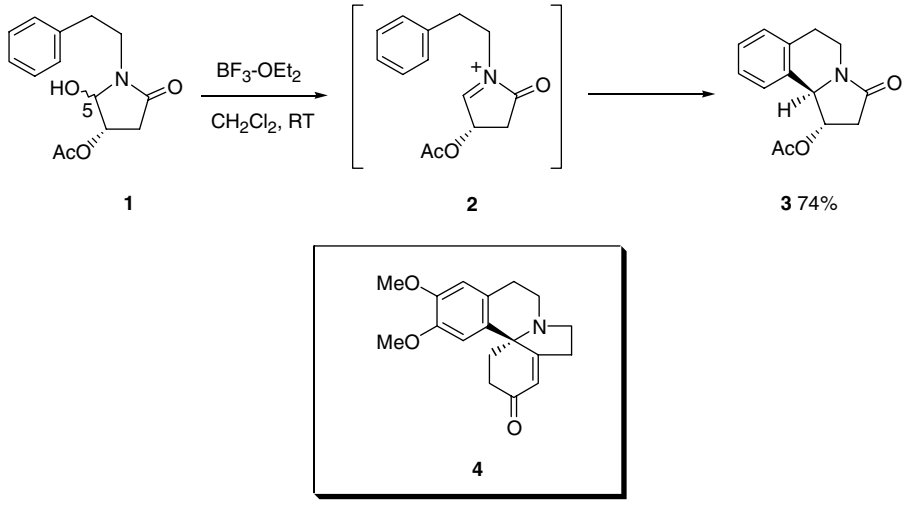
Abstract—The stereochemical outcome of *N*-acyliminium ion mediated cyclisations of malic acid derived lactams depend upon the nature of the protecting group on the lactam secondary alcohol, and also on the nature of the substituent at the reacting electrophilic centre. The origins of an unusual *syn*-selective cyclisation of a TIPS protected lactam are discussed, and the cyclisation is employed as the key step in an asymmetric synthesis of 3-demethoxyerythratidinone (**4**).

N-Acyliminium ions have proved to be especially useful reactive intermediates for alkaloid synthesis, enabling controlled C–C bond formation in both intra- and inter-molecular modes with a range of nucleophilic species.[1] In connection with our programme of research exploring new asymmetric routes to erythrinan alkaloids we became interested in comparing our recently established chiral base mediated (enantioselective) approach to a related enantiospecific method using (*S*)-malic acid as starting material.[2] Previously, Lee and co-workers had described a synthesis of pyrrolidinoisoquinoline derivatives that used the cyclisation of hydroxylactam **1** to give the tricyclic product **3** as a single diastereoisomer, Scheme 1.[3]



Scheme 1. Stereocontrolled *N*-acyliminium arylation.

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In this example, as in many related ones, the stereochemical outcome results from nucleophilic attack *anti* to the bystander acetoxy group, which may be influencing the outcome by neighbouring group participation.[4]

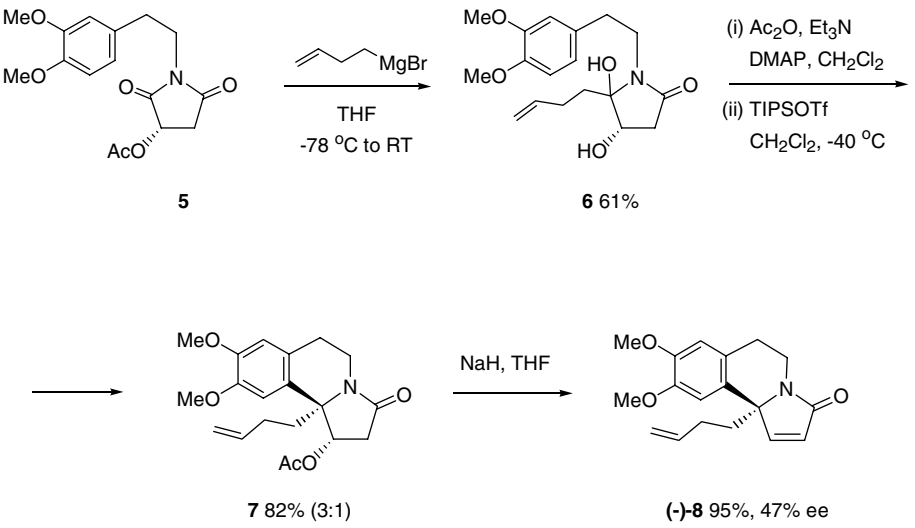
In this Letter, we describe how we have employed this type of process in the synthesis of the naturally occurring alkaloid (+)-3-demethoxyerythratidinone **4**,[5,6] and also demonstrate that: (i) more highly substituted hydroxylactams related to **1** may not give the high level of control seen in Scheme 1; (ii) switching from acetate protection to TIPS protection for the ring hydroxyl can enable the *opposite* sense of diastereocontrol to that shown in Scheme 1—but this depends upon the substituent present at C-5.

Our synthesis began with the addition of but-3-enylmagnesium bromide to the readily available enantiopure imide **5**,[7] which gave hydroxylactam **6** in a completely regiocontrolled fashion, Scheme 2.

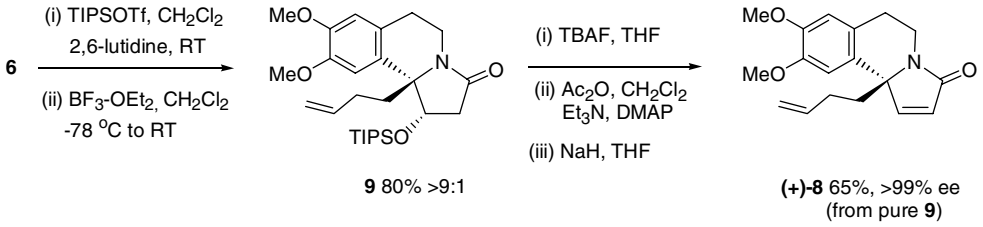
This outcome was expected based on a closely related Grignard addition described previously in which the ring acetate was retained in the product.[8] In our case, the use of a large excess of Grignard reagent (5 equiv) gave optimal yields but also deacylated the secondary alcohol. This proved of little consequence at this stage since acetylation of **6** re-installed the secondary acetate without affecting the tertiary hydroxyl function. This hydroxylactam, on treatment with TIPSOTf, gave the tricyclic lactam **7** in good yield but with a very modest diastereomer ratio of 3:1. This outcome was disappointing and somewhat surprising based on the precedent illustrated in Scheme 1. Lactam **7** could be converted into the unsaturated counterpart **8** by treatment with base and the enantiomeric excess of 47% of this product reflected the low diastereomer ratio of the precursor.[9]

The selectivity issue in the cyclisation leading to **7** could not be resolved by the use of lower reaction temperatures since the reaction proved very sluggish below −40 °C, and the use of Lewis acids such as BF_3–OEt_2 gave similarly modest selectivity to TIPSOTf. We reasoned that exchanging the ring acetate substituent for a rather bulky TIPS protecting group might enhance the facial selectivity in the *N*-acyliminium reaction. However, a Grignard addition reaction of an *O*-silyl imide counterpart of **5** had previously been shown to occur with low regioselectivity, and so starting with a silicon protected imide was unattractive.[10] Thus, the combined addition and in situ hydroxyl deprotection represented by the conversion of **5** into **6** now proved helpful in combining the high regiocontrol of the acetate protected series with the opportunity to swap for a silyl protected derivative in the pursuit of high diastereocontrol in the subsequent cyclisation. With this plan in place the modified synthetic sequence is shown in Scheme 3.

Protection of **6** as the corresponding secondary TIPS ether proved straightforward and exposure of this



Scheme 2. *N*-acyliminium arylation with modest stereocontrol.



Scheme 3. *N*-acyliminium arylation with high and reversed stereocontrol.

product to BF_3–OEt_2, as described by Lee (Scheme 1),[3] but initially at low temperature, then gave a cyclised lactam in good yield and in at least 9:1 selectivity. To our initial surprise, the product of this reaction was **9**, having a pseudo-diastereomeric relationship to **7** from the acetate series, in which aromatic attack on the putative *N*-acyliminium intermediate occurred from *the same side of the lactam ring as the OTIPS substituent*.

The stereochemical assignment of the lactam **9** was secured following an X-ray structure determination, Figure 1.[11]

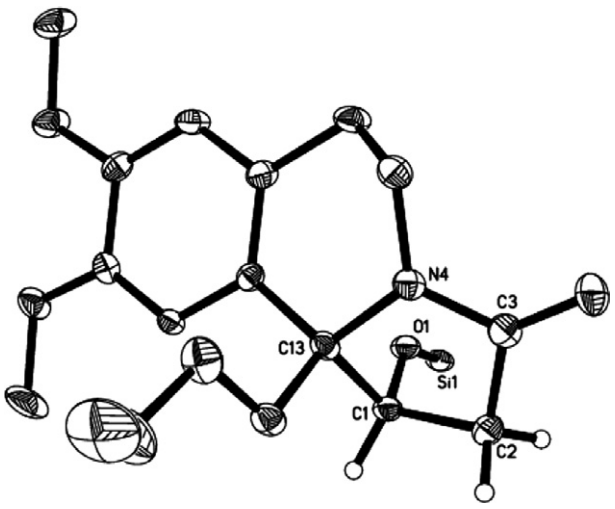
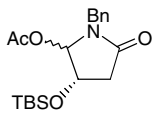


Figure 1. X-ray structure of **9** illustrating attachment of the aromatic group *syn* to the *O*-silyl substituent. Only one of four crystallographically independent molecules is shown, and the ellipsoids are drawn at the 30% probability level. The ^{i}Pr substituents on the TIPS group, and most of the hydrogen atoms, have been omitted for clarity.

Compound **9** was accompanied by small amounts (up to 10% but usually less) of the corresponding minor diastereomer, which was easily separated by chromatography, and both of which were used in subsequent chemistry (vide infra). By removing the silicon protecting group, acetylating the so-formed alcohol and elimination of acetic acid as before, diastereomerically pure **9** was converted into enantiomerically pure (+)-**8**.



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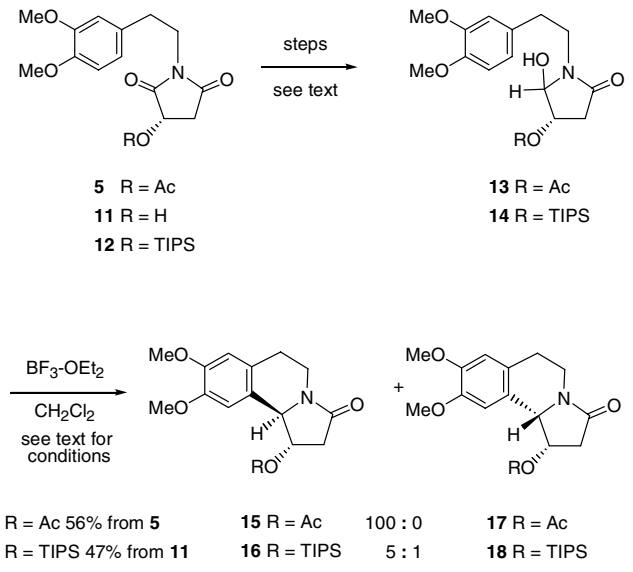
High *syn*-selectivity has been reported previously for intermolecular reactions of the acetoxylactam **10** with allyl, propargyl and allenylsilanes, and stannanes, under Lewis acid catalysis, with product ratios ranging from 3.8:1 to >100:1.[12] This 'remarkable cis-selectivity' was attributed to a stereoelectronic effect involving preferred *anti* alignment of the existing C–O σ bond and the emerging σ* orbital at the reacting centre. In contrast, the reactions of **10** involving enol silanes and other silicon-based nucleophiles seem to give rather modest selectivities in most cases.[13]

This, slightly mysterious, '*syn*-effect' appears not to have been observed before in intramolecular closures of the type we have described, or indeed with any systems involving aromatics as nucleophiles.[14] If stereoelectronics were responsible for our cyclisation outcome we expected to be able to generalise the result and achieve similar selectivities using lactams with other substituents.

We chose to examine the parent system analogous to that shown in Scheme 1, in which the C-5 substituent is simply a hydrogen, Scheme 4.

For direct comparison with the result in Scheme 1 we first converted **5** into **13** by reduction with $NaBH_4$ in CH_2Cl_2–MeOH, and then carried out the cyclisation using BF_3–OEt_2 in CH_2Cl_2 between 0 °C and room temperature. In accord with previous results, including that in Scheme 1, only a single diastereomeric product, lactam **15**, resulting from the expected *anti*-attack was obtained (in 56% yield for two steps).

We then prepared the OTIPS derivative **14** in order to test for the '*syn*-effect', which required routine conversions of **5** into **11** by acidic hydrolysis (86%), protection to give **12** and then $NaBH_4$ reduction to give **14**. Cyclisation of this compound using BF_3–OEt_2 in CH_2Cl_2 was carried out at the lowest viable temperature, −40 °C to rt, so as to mimic the conditions in Scheme 3, and maximise selectivity. The cyclisation gave two diastereomeric products **16** and **18** in which the former compound, arising from *anti*-addition predominated. This is the same sense of selectivity as the acetate series, and demonstrates that whatever is responsible for the *syn*-selectivity leading to the butenyl derivative **9** does not seem to



Scheme 4. *N*-acyliminium cyclisation of the parent lactam.

operate for the parent system where the C-5 substituent is simply a proton.

A more detailed analysis of this system must await further results, but at present a most likely explanation for the selective formation of **9** is based on a conformational relay effect as illustrated in Figure 2.[15]

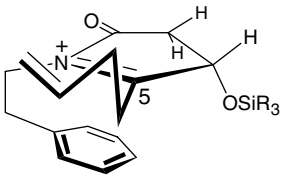


Figure 2.

Examination of molecular models suggests that the arrangement shown is a reasonable representation of the reactive conformation of the intermediate *N*-acyliminium ion. The presence of the very bulky TIPS group (R = ^{i}Pr) pushes the butenyl group to the opposite (top) face of the lactam ring, which in turn engenders attack of the aromatic group from the same side as the OTIPS substituent. Reaction in the opposite sense requires a more congested arrangement.

In the simpler system, where the C-5 substituent is a proton, the relay effect is lost and reaction is more facile *anti* to the OTIPS group (although by no great measure since the selectivity is modest).

With an efficient and selective access to **9** available we were then in a position to conclude our proposed new access to 3-demethoxyerythratidinone **4**. Initially, in order to match our synthetic material with the alkaloid *in the natural enantiomeric series* we used the *minor* product generated from the cyclisation shown in Scheme 3— that is, the diastereomer of **9** (**19**), Scheme 5.[16]

Wacker oxidation of diastereomerically pure **19** gave ketolactam **20** in good yield and subsequent reduction with $LiAlH_4$–$AlCl_3$ served to remove the unwanted amide carbonyl and effect removal of the silicon protecting group. Diol **21** had been prepared previously by Wasserman and Amici in their synthesis of racemic 3-demethoxyerythratidinone,[6d] and application of the final two steps from their synthesis to **21** involved double Swern oxidation to give **22** and then aldol cyclisation to give (+)-3-demethoxyerythratidinone **4**. The spectroscopic data for this compound were consistent with the structure shown and previous published data.[17]

As anticipated, the use of **19** as starting material resulted in the formation of the final alkaloid as its natural antipode—$[\alpha]_D^{26}$ +316 (*c*, 0.4, $CHCl_3$), comparison data[5]—$[\alpha]_D^{20}$ +325 (*c*, 0.25, $CHCl_3$). When we applied the same sequence of reactions shown in Scheme 5 to the diastereomeric starting lactam **9** we obtained very similar yields for each step (in parentheses) and were able to access the natural product as the unnatural (−)-antipode.

In summary, these new results help to clarify the stereochemical issues related to *N*-acyliminium ion reactions of malic acid derived lactams, and particularly the unusual *syn*-effect seen with a TIPS protected compound. The synthesis of (+)-3-demethoxyerythratidinone represents only the third asymmetric access to this compound, and at eight steps from commercial material is one of the shortest of any of the routes established to date.

Acknowledgement

We gratefully acknowledge the University of Nottingham and the ORS scheme for support of this work through a studentship to F.Z.

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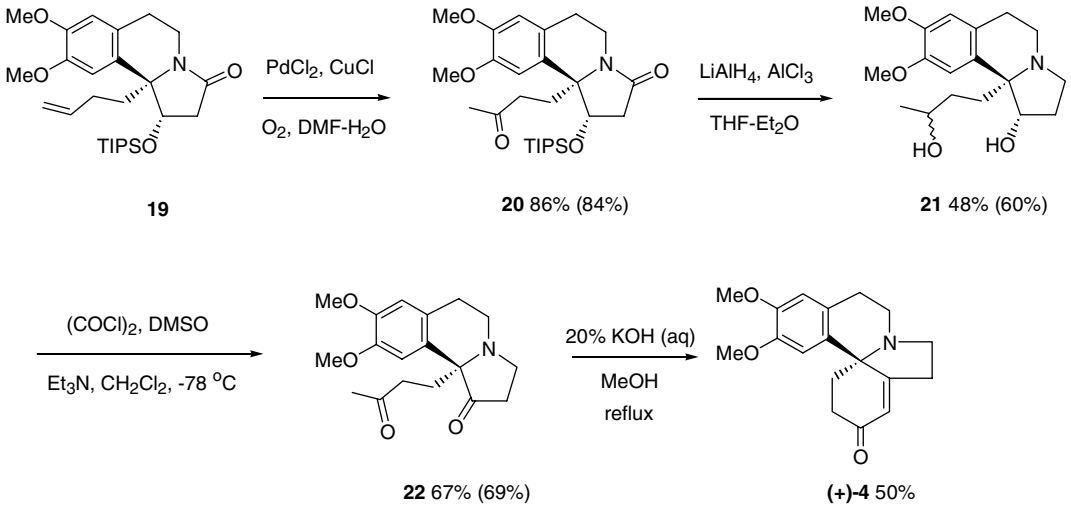

Scheme 5. Synthesis of (+)-3-demethoxyerythratidinone.

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15. Pilli has proposed a somewhat similar explanation for reactions of related regioisomeric lactams, see: Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1973.
16. Experimental and compound data for Scheme 5: *Ketolactam* **20**: $PdCl_2$ (61 mg, 0.34 mmol) and CuCl (171 mg, 1.7 mmol) were dissolved in a mixture of DMF (8 mL) and water (1.5 mL), the reaction mixture was stirred at rt for 2 h. Then lactam **19** (818 mg, 1.7 mmol) in DMF (3 mL) was added and the resulting solution was stirred under an O_2 atmosphere for 20 h. The product was then extracted with ether (150 mL) and washed with water (10 mL) twice and brine (10 mL). The organic extract was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on a silica column (eluent: PE/AcOEt = 1:1) to give the methyl ketone **20** (731 mg, 86%) as a sticky oil $[\alpha]_D^{26}$ −78.6 (*c* 1.55 in $CHCl_3$) IR ($CHCl_3$): 2936, 2868, 1714, 1682, 1457, 1361, 1113, 1069, 996, 883 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$–1.10 (m, 21H, $CH(CH_3)_2$), 2.00 (s, 3H, CH_3CO), 2.18–2.24 (m, 3H, $COCH_AH_BCH_2$), 2.54–2.78 (m, 5H, $ArCH_2$, CH_2CON, $COCH_AH_BCH_2$), 2.85 (td, $J = 4$, 12 Hz, 1H, NCH_AH_B), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.31 (dd, $J = 5$, 9 Hz, 1H, NCH_AH_B), 4.41 (t, $J = 9.6$ Hz, 1H, CHOTIPS), 6.48 (s, 1H, ArH), 6.80 (s, 1H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 12.4$ (SiCH), 17.6 (CH_3), 17.7 (CH_3), 17.8 (CH_3), 17.9 (CH_3), 28.2 ($ArCH_2$), 29.8 ($COCH_3$), 30.0 (CCH_2), 34.9 ($ArCH_2CH_2$), 38.9 (CH_2COMe), 40.6 ($NCOCH_2$), 55.6 (OCH_3), 55.7 (OCH_3), 66.2 (C), 75.9 (CHOSi), 107.8 (ArCH), 111.4 (ArCH), 124.6 (ArC), 132.2 (ArC), 147.83 (ArC), 147.81 (ArC), 169.4 (C=O), 207.1 (C=O). HR-EIMS: *m/z* Calcd for $C_{27}H_{43}NO_5Si(M^+ + H)$: 490.2989; found, 490.2990.
Diketone **22** via diol **21**: A solution of $AlCl_3$ (1.5 g, 11 mmol) in Et_2O (10 mL) was added dropwise to a solution of $LiAlH_4$ (11 mL, 1 M in THF) at −15 °C, then the resulting solution was stirred at rt for 1 h. Then the above solution was added dropwise to a solution of lactam **20** (600 mg, 1.2 mmol) in THF (10 mL) at −15 °C. The resulting reaction mixture was stirred overnight before quenching by careful addition of 5% NH_3 (aq). The product was extracted into EtOAc (200 mL) and washed with water (10 mL) and brine (10 mL). The organic extract was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on a silica column (eluent: PE/AcOEt = 4:1 then 2:1) to give the diol **21** (189 mg, 48%) as a colourless oil. This epimeric mixture of products was used directly in the next step.
A solution of $(COCl)_2$ (95 mg, 0.75 mmol) in DCM (2 mL) under a nitrogen atmosphere was cooled to −78 °C, and then DMSO (0.11 mL, 1.5 mmol) was added dropwise, and the resulting solution was stirred at this temperature for 30 min. Diol **21** (60 mg, 0.19 mmol) in DCM (2 mL) was added dropwise, then the reaction mixture was stirred at −78 °C for 2 h. Et_3N (0.38 mL, 2.8 mmol) was added dropwise, the reaction mixture was warmed to room temperature, and then water (5 mL) was added. The product was extracted into DCM (30 mL), the organic phase was washed with water (5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$ and then concentrated. The crude product was purified by flash chromatography on a silica column (eluent: PE/AcOEt = 1:2) to give **22** as a colourless oil (40 mg, 67%). $[\alpha]_D^{25}$ 50.2 (*c* 0.75 in $CHCl_3$). IR ($CHCl_3$): 2936, 2850, 1746, 1709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.11$ (s, 3H, CH_3CO), 2.11–2.26 (m, 3H, $CH_2CH_AH_B$), 2.35–2.43 (m, 3H, CH_2CO, $ArCH_AH_B$), 2.48–2.54 (m, 1H, $CH_2CH_AH_B$), 3.00–3.10 (m, 4H, $ArCH_AH_BCH_AH_BNCH_2$), 3.14–3.22 (m, 1H, $ArCH_2CH_AH_BN$), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.51 (s, 1H, ArH), 6.90 (s, 1H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 21.1$ (CH_2), 30.2 (CH_3), 32.6 (CH_2), 36.3 (CH_2), 39.2 (CH_2), 41.3 (CH_2), 43.5 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 68.1 (C), 109.6 (ArCH), 111.6 (ArCH), 125.0 (ArC), 126.0 (ArC), 147.6 (ArC), 148.2 (ArC), 208.0 (C=O), 215.9 (C=O). HR-EIMS: *m/z* Calcd for $C_{18}H_{23}NO_4Na(M^+ + Na)$: 340.1515; found, 340.1519.
(+)-3-demethoxyerythratidinone **4**: A solution of diketone **22** (34 mg, 0.107 mmol) and 20% KOH (1.5 mL) in MeOH (30 mL) was heated at 120 °C under a nitrogen atmosphere for 10 h. The mixture was cooled and then concentrated and extracted with DCM (20 mL), the organic phase was then washed with water (5 mL) and brine (5 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on a silica column (eluent: DCM/MeOH = 10:1) to give (+)-**4** as a yellow oil (15.9 mg, 50%). $[\alpha]_D^{26}$ +316 (*c* 0.4 in $CHCl_3$). IR ($CHCl_3$): 2936, 2852, 2399, 1666, 1463, 1360, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.24$–2.33 (m, 2H, CCH_2), 2.43–2.68 (m, 4H, CH_2CO, $CH_AH_BC=$), 2.68–2.92 (m, 2H,

NCH_AH$_B$CH$_A$H$_B$C=), 3.03–3.12 (m, 2H, ArCH_AH$_B$CH$_2$-NCH_AH$_B$), 3.26 (dd, 1H, $J = 7.6$, 14.4 Hz, NCH_AH$_B$), 3.45–3.52 (m, 1H, NCH$_A$H$_B$), 3.76 (s, 3H, OCH$_3$), 3.88 (s, 3H, OCH$_3$), 6.12 (s, 1H, CH=), 6.56 (s, 1H, ArH), 6.66 (s, 1H, ArH). ^{13}C NMR (100.6 MHz, CDCl$_3$): $\delta = 21.5$ (ArCH$_2$), 28.6 (*C*H$_2$C=), 32.8 (*C*H$_2$CO), 35.9 (C*C*H$_2$), 40.1 (ArCH$_2$*C*H$_2$N), 45.7 (N*C*H$_2$CH$_2$C=), 55.9 (OCH$_3$), 56.0 (OCH$_3$), 63.7 (C), 110.2 (ArCH), 112.8 (ArCH), 123.9 (*C*H=C), 124.4 (ArC), 125.4 (ArC), 146.9 (ArC), 148.4 (ArC), 168.5 (C=), 199.3 (C=O). HR-EIMS: *m*/*z* Calcd for C$_{18}$H$_{22}$NO$_3$(M$^+$+H): 300.1594; found, 300.1586.

17. Despite the natural product having been prepared a number of times there are scant data readily available in the literature because so many reports concern formal syntheses that converge on late Tsuda intermediates, see Ref. 6.